A Dissertation for the Degree of Doctor of Philosophy in Pharmacy

Total Syntheses of Wondonins and Isowondonins Based on a Biosynthetic Pathway

생합성 예상 경로를 기반으로 한 **Wondonins**과 **Isowondonins**의 전합성

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Abstract

The first total syntheses of wondonins and isowondonins, which are unusual imidazole marine alkaloids, has been accomplished through the development of methods for the selective formation of styryl sulfate group and regioselective alkylation of the imidazole. Application of the Noyori asymmetric hydrogenation of ketones allows the asymmetric synthesis of isowondonins. These results in conjunction with ECD calculations led to the determination of the absolute configuration of isowondonins.

Key word: Angiogenesis, *E*/*Z*-Selective styryl sulfate formation, Regioselective imidazole alkylation, Noyori asymmetric hydrogenation, Total synthesis

Student Number: 2009-24033

Preface

Citations from previously published work in this thesis are as follows:

Contents

I. Introduction

From an association of the sponges *Poecillatra wondoensis* and *Jaspis sp*., four bis(dihydroxystyrenyl) imidazole marine alkaloids (**1**–**4**, Figure 1) were isolated by one of us and named wondonins and isowondonins according to the configuration of the styryl double bond.[1] The planar structure was determined by various spectroscopic methods. However, the relative and absolute stereochemistry of C1 and C2 could not be determined because of the lack of reliable NOE correlations.

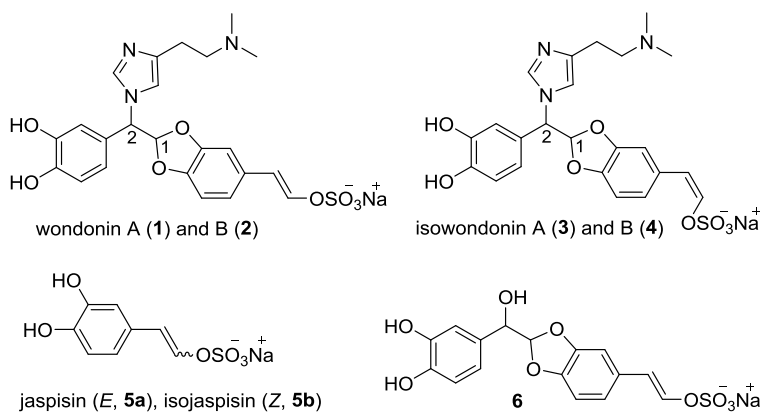


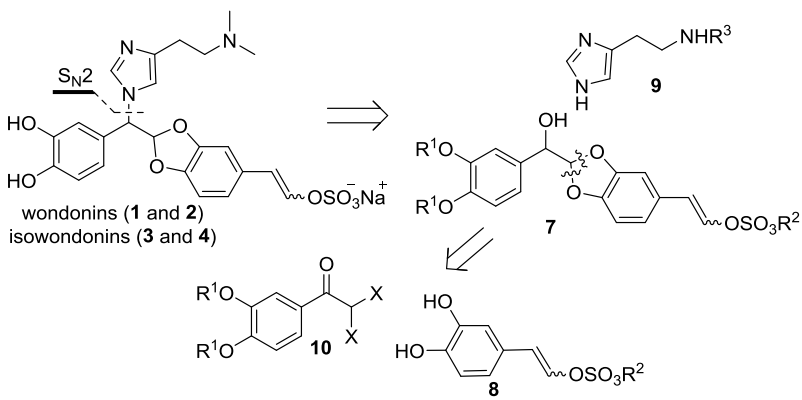
Figure 1. Structures of wondonins (**1**, **2**), isowondonins (**3**, **4**) and other styryl sulfate natural products.

The wondonin family is structurally unique by virtue of its dimeric dihydroxystyrenyl skeleton with a five-membered acetal ring and an embedded

styryl sulfate moiety. These marine alkaloids exhibit interesting biological activities, including antiangiogenic activity.[1,2] For example, wondonins inhibited the tube formation of human umbilical vein endothelial cells induced by bFGF or hypoxia without overt cytotoxicity,[1a,2] which are unique and useful characteristics for the development of new angiogenesis inhibitors with fewer side effects and less toxicity. Because of their unique structural and biological properties, wondonins have high potential to become a new class of antiangiogenic therapeutic agents. However, these natural products, like others, have many hurdles to clear. One challenge is the very restricted availability of the natural source. Chemical synthesis is the most likely solution for securing materials for further biological investigations.

Because jaspisins **5**[3] and the unnamed natural product **6** (Figure 1) were also identified during the process of isolating **1**–**4**,[1b] the wondonin family may originate biosynthetically from **6**, which in turn is formed from jaspisins **5**. According to this plausible biosynthetic pathway, our synthetic route to **1**–**4** was planned as shown in Scheme 1. with the preparation of dimeric dihydroxystyrene **7** from styryl sulfate **8** in the early stage of synthesis, followed by its combination with histamine moiety **9**.

Scheme 1. Retrosynthetic analysis of wondonins and isowondonins



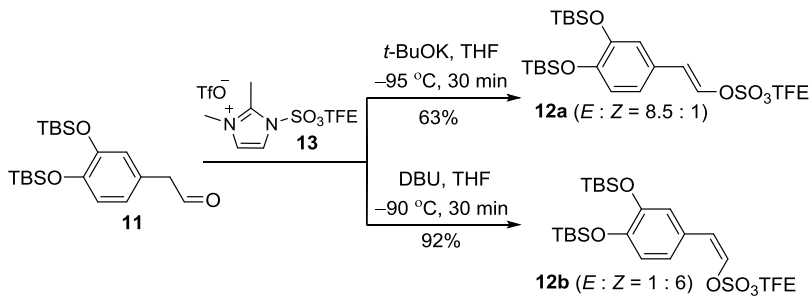
One of the major synthetic challenges afforded by members of the wondonin family includes the preparation of the styryl sulfate moiety. Although several natural products with a styryl or vinyl sulfate moiety have been reported,[3,4] synthetic methods to access these functional groups are very limited and suffer from low yields.[5] The available method for the preparation of vinyl sulfate is based on the use of an elimination reaction to form a vinyl residue from an α-chloro *O*-sulfated substrate[5c] or a cyclic sulfate.[5a,b] The application of this elimination method to the total synthesis would compel the introduction of the vinyl sulfate moiety at a late synthetic stage because of its instability and high polarity. This strategy may cause several difficulties during the total synthesis, including intensive and careful manipulation of protecting groups. Therefore, we chose an

early-stage introduction of the styryl sulfate in a protected form followed by removal of the protecting group for sulfate at the end of the synthesis.

II. Results and Discussion

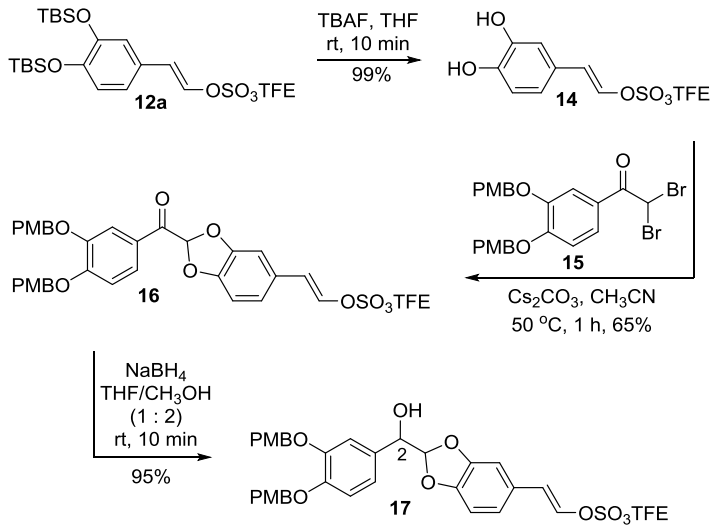
Our total synthesis started with an investigation of methods for the facile and stereoselective formation of the styryl sulfate group. Inspired by the facile synthesis of vinyl tosylates or vinyl triflates from the corresponding carbonyl compounds *via* enol intermediates,[6] we envisioned that trapping of the enolate from α-aryl aldehyde **11** (Scheme 2) with a suitable sulfating agent would afford the desired styryl sulfate in a protected form. As a protecting group for sulfate, we chose 2,2,2-trifluoroethyl (TFE) group because sulfate esters with this protecting group are sufficiently stable under a variety of conditions to allow multistep synthesis with it.[7] Attempts at transforming α-aryl aldehyde **11** into styryl sulfate **12** were not successful[8] until sulfuryl imidazolium salt **13**[9] was employed as the sulfating agent. When *t*-BuOK was used as a base in THF at –95 ℃, desired styryl sulfate **12a** was obtained in a ratio of 8.5:1 strongly favoring the *E*-isomer. However, when DBU was used, *Z*-isomer **12b** was the major product in a ratio of 1:6 (*E*/*Z*). The *E*/*Z* geometric selectivity was highly dependent on the reaction temperature and the types of bases.[8]

Scheme 2. Syntheses of styryl sulfate **12a** and **12b**



The obtained sulfates **12a** and **12b** were taken forward to the corresponding natural products. For the synthesis of wondonins **1** and **2** with *trans*-styryl sulfate **12a**, the silyl protecting group of **12a** was removed with TBAF to yield **14** (Scheme 3). The obtained catechol **14** was condensed with α,α'-dibromoketone **15** in the presence of Cs_2CO_3 at 50 ℃[10] to afford dimeric dihydroxystyrene **16**. It is noteworthy to note that the vinyl sulfate group decomposed when the reaction temperature exceeded 50 ℃. The ketone of **16** was reduced to a hydroxyl group with $NaBH_4$ to afford **17** in good yield. Both the C2α-OH and C2β-OH isomers of **17** were formed in equal ratio. The two resulting diastereomers were inseparable by column chromatography. Therefore, we proceeded with the mixture of diastereomers.

Scheme 3. Synthesis of dimeric dihydroxystyrenyl compound **17**

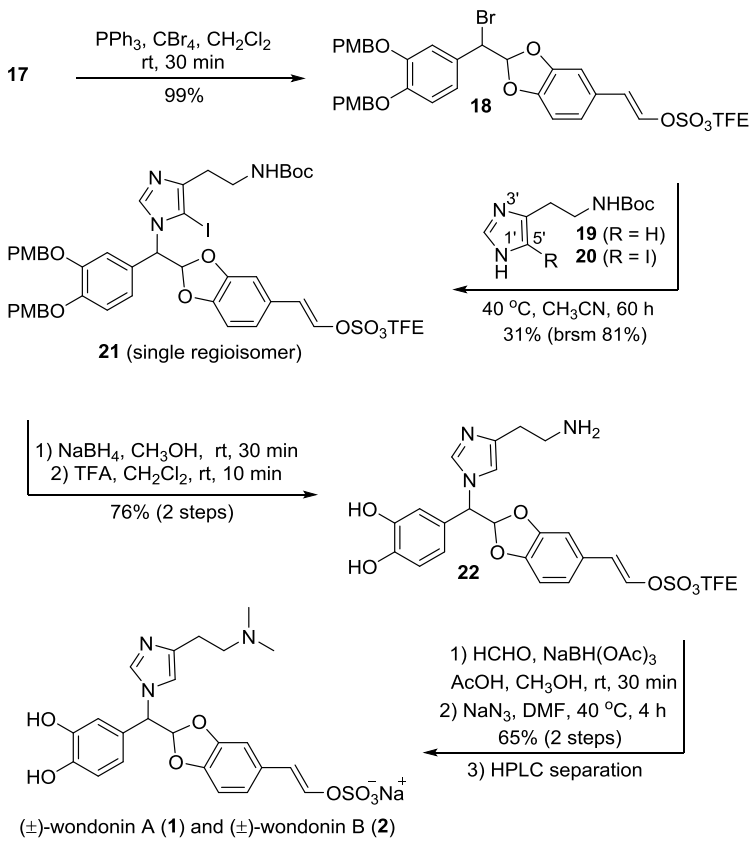


Having obtained the dimeric dihydroxystyrenyl skeleton, we next explored the introduction of the histamine moiety at the C2 position (Scheme 4). The C2 hydroxyl group of **17** was converted to a bromide under Appel conditions[11] to yield **18**. When the substitution reaction of **18** was carried out with N-Boc protected histamine **19** in CH_3CN at 40 ℃, a mixture of regioisomeric products were obtained in a 1:1 ratio due to the tautomeric equilibrium of the imidazole ring.[8] The addition of base to the reaction caused the decomposition of **18**. To overcome the regioselectivity problem, we investigated directing groups that could differentiate two nitrogen atoms in the imidazole ring and can be easily removed after the reaction. After some efforts, we determined that an iodine group at the 5'-position was suitable for this purpose. When the substitution reaction was performed with

iodinated histamine **20**[12] in CH_3CN at 40 ℃ for 60 h, compound **21** was obtained as the only detectable regioisomer (31% yield, 81% brsm). At a higher temperature, the vinyl sulfate moiety decomposed, and a complex mixture was obtained. To understand the obtained regioselectivity, a DFT study was performed. The calculated "relative nucleophilicity"[13] values of the two nitrogens in **20** differed considerably (N1' = 3.5, N3' = 0.7) compared to those of the two nitrogens in **19** (N1' = 0.3, N3' = 0.5).[14]

The iodine-directing group was removed by $NaBH_4$, and the N-Boc and PMB protecting groups were simultaneously removed using trifluoroacetic acid to afford **22** in 76% yield for two steps. The *N*,*N*-dimethylation of the primary amine function in **22** was achieved by treatment with formalin and $NaBH(OAc)_3$. Finally, the TFE protecting group of sulfate was removed by employing NaN_3 in DMF[9] to afford a mixture of **1** and **2** (65% for two steps). At this stage, the two diastereomers (**1** and **2**) were separated by semi-preparative HPLC. The obtained spectra for each isomer were essentially identical to those of natural wondonin A and B.[8]

Scheme 4. Completion of the syntheses of (±)-wondonin A (**1**) and (±)-wondonin B (**2**)

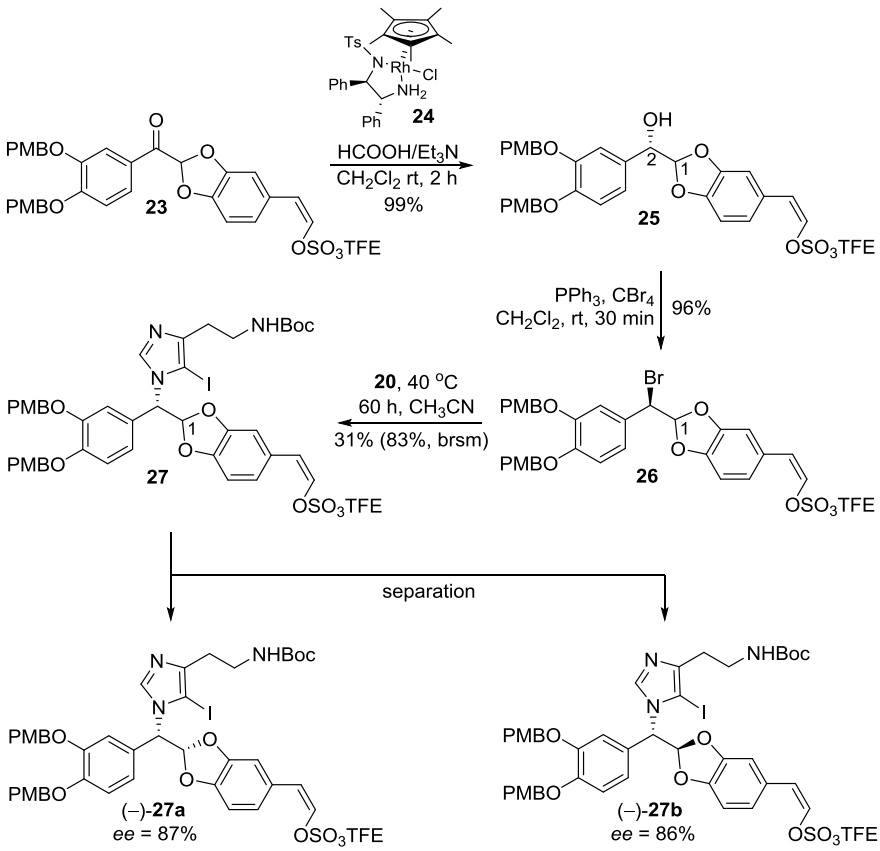


After accomplishing the synthesis of wondonins, we synthesized isowondonins from *cis*-styryl sulfate **12b**. For the assembly of isowondonins, we used the same sequence of reactions as applied to the synthesis of wondonins. The diastereomeric mixture of isowondonins was obtained in a similar overall yield. The spectra of the HPLC-separated isomers were also in good agreement with those of natural

isowondonin A and B.[8]

For the asymmetric synthesis, we initially focused on the installation of the chiral center at the methylenedioxy carbon position (C1). Due to the lack of availability of these asymmetric methods, these attempts were not successful. On the other hand, early-stage modification in this racemic synthetic route permitted the asymmetric synthesis of isowondonins (Scheme 5). When the ketone of (±)-**23** was subjected to the action of Noyori's (*R*,*R*)-RhTsDPEN catalyst **24** under transfer hydrogenation conditions,[15] the corresponding alcohol **25** was afforded in 99% yield in a ratio of 19:1 in favor of the (*S*)-configuration at C2.[16] At this stage, the two diastereomers resulting from mixed stereochemistry at C1 were inseparable. The separation of diastereomers was possible using Prep-HPLC after the formation of histamine moiety attached compound **27**. The separated diastereomers **27a** and **27b** both showed a negative optical rotation. The enantiomeric purity (ee) was de termined by chiral HPLC analysis to be 87% and 86% for (−)-**27a** and (−)-**27b**, respectably. These percentages correspond to a ratio of 19:1, which indicated the conservation of the enantiomeric purity at C2 in the two successive substitution reactions (**25**→**27**).

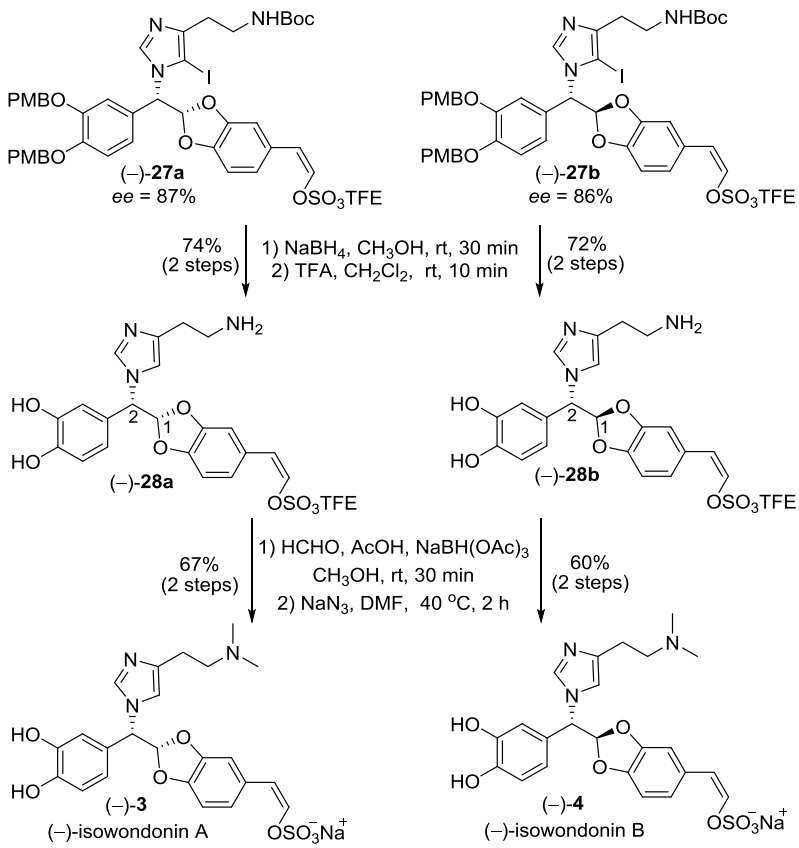
Scheme 5. Synthesis of compounds (–)-**27a** and (–)-**27b**



The remaining steps in the synthesis of isowondonins mirrored those of the racemic synthesis (Scheme 6). The synthetic isowondonin from (–)-**27a** exhibited a negative optical rotation {$[\alpha]^{20}_{D}$ –4.2 (*c* 0.72, CH_3OH)}, and its NMR spectra was in good agreement with those of isowondonin A. In addition, the one from (–)-**27b** also exhibited a negative rotation {$[\alpha]^{20}_{D}$ –4.5 (*c* 0.65, CH_3OH)}, and the spectra were identical to those of isowondonin B. The reported optical rotations of

isowondonins A and B are both negative ({$[\alpha]^{20}_D$ –4.0 (*c* 0.72, CH_3OH)} and {$[\alpha]^{20}_D$ –3.7 (*c* 0.65, CH_3OH)}). These observations suggested that isowondonins A and B possess an (*S*) configuration at C2 and are epimers at the C1 acetal position.

Scheme 6. Completion of the syntheses of (–)-isowondonin A (**3**) and (–)-isowondonin B (**4**)



After determining the C2 configuration of the isowondonins, electronic circular dichroism (ECD) spectroscopy was used to define the configuration of C1.[17] Because the experimental ECD spectrum of isowondonins was not suitable, the ECD analysis was performed using compound **28**. Theoretical calculations of the ECD spectrum were conducted for all four possible enantiomers of **28a** and **28b** using time-dependent DFT at the B3LYP/SVP level in methanol. As shown in Figure 2, the calculated ECD spectrum of the (1*S*,2*S*)-isomer exhibited good agreement with the experimental spectrum of (–)-**28a** in methanol, and the spectrum of the (1*R*,2*S*)-isomer was in good agreement with the experimental curve of (–)-**28b**.[18] Therefore, the stereochemistry of isowondonins A and B was assigned as shown in Scheme 6.

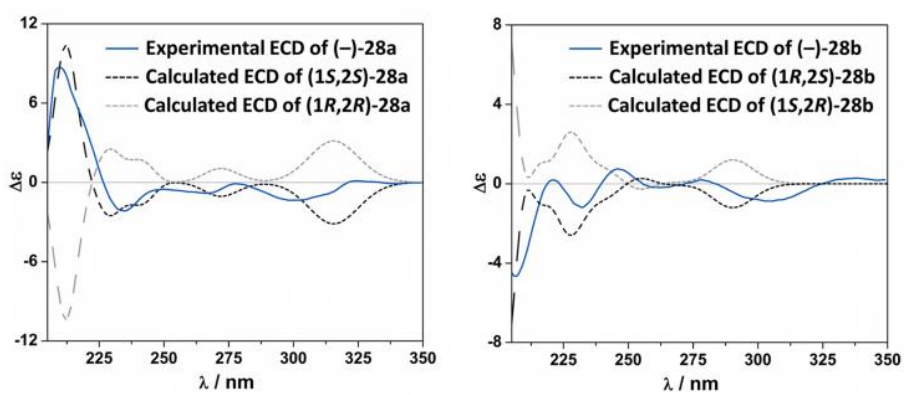


Figure 2. Experimental and calculated ECD spectra of (–)-**28a** and (–)-**28b**.

III. Conclusion

In summary, we have completed the first total synthesis of bis(dihydroxystyrenyl) imidazole marine alkaloids. The biomimetic synthesis of wondonins and isowondonins was achieved using a convergent strategy. Key aspects of the synthesis include the selective formation of styryl sulfate in a protected form and the regioselective alkylation of the iodinated imidazole. In the asymmetric synthesis of isowondonins, Noyori's asymmetric hydrogenation was employed to install the stereocenter at C2. In combination with the asymmetric synthesis, ECD calculations enabled us to determine the stereochemistry of the isowondonins.

IV. Experimental

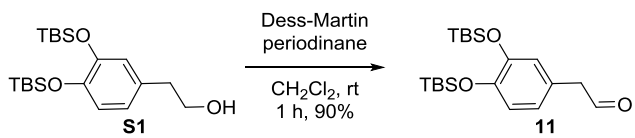
General.

All of the chemicals were reagent grade and used as purchased. All of the reactions were performed in an inert atmosphere consisting of dry argon or nitrogen using distilled dry solvents. The reactions were monitored by thin layer chromatography (TLC) analysis using silica gel 60 F-254 TLC plates. The compound spots were visualized using UV light (254 nm). The melting points were measured using a Buchi B-540 melting point apparatus without correction. Flash column chromatography was carried out on silica gel (230–400 mesh). The optical rotations were measured using sodium light (D line 589.3 nm) at 20 ℃. ^{1}H NMR (800, 600, 500, 400 or 300 MHz) and ^{13}C NMR (200, 150, 125, 100, or 75 MHz) spectra were referenced to Me_4Si (0 ppm), residual $CHCl_3$ (^{1}H NMR δ = 7.24 ppm, ^{13}C NMR δ = 77.16 ppm), and CD_3OD (^{1}H NMR δ = 3.30 ppm, ^{13}C NMR δ = 49.00 ppm). The splitting patterns are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and brs (broad singlet) for the ^{1}H NMR data. The ECD spectra were acquired on an Applied Photophysics Chirascan-Plus circular dichroism spectrometer. The IR spectra were measured on a Fourier Transform Infrared spectrometer. The high-resolution mass spectra (HRMS) were recorded using fast atom bombardment (FAB) or electrospray ionization (Q-TOF). HPLC

was performed on an Agilent 1200 series instrument with a UV detector and CHIRALCEL OD-H column (0.46 × 25 cm).

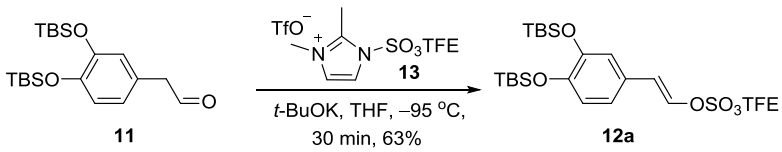
IV-1. Synthesis of (±)-wondonin A (1) and B (2)

2-(3,4-bis((*tert*-butyldimethylsilyl)oxy)phenyl)acetaldehyde (11)



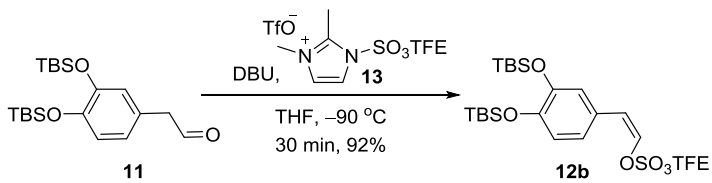
Dess-Martin periodinane (5.00 g, 11.8 mmol) was added to a solution of S1[19] (4.40 g, 11.5 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at rt for 1 h. After the starting materials disappeared by monitoring with TLC, water was added. Then, the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (silica gel, gradient from 20:1 to 10:1 hexane/EtOAc) afforded **11** (3.94 g, 90%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.66 (t, *J* = 2.6 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.63 (dd, *J* = 10.2, 2.1 Hz, 2H), 3.50 (d, *J* = 2.5 Hz, 2H), 0.96 (s, 18H), 0.18 (s, 6H), 0.17 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.6, 147.2, 146.3, 124.6, 122.5, 122.4, 121.4, 49.8, 25.9, –4.0; IR υ_{max} (neat, cm^{-1}) 2934, 2861, 1729, 1511, 1253, 835.

(*E*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)styryl (2,2,2-trifluoroethyl) sulfate (12a)



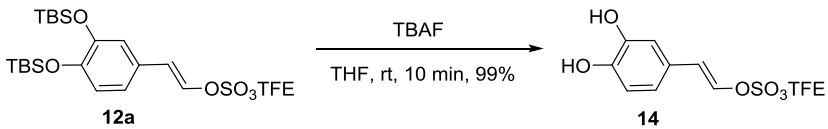
A solution of aldehyde **11** (50.0 mg, 0.131 mmol) in THF (1 mL) was cooled to –95 ℃ (cooling bath with using liquid nitrogen and CH_3OH), followed by the addition of the solution of potassium *tert*-butoxide in THF (1.0 M, 0.262 mL, 0.262 mmol). The reaction mixture was stirred at –95 ℃ for 10 min. Then sulfuryl reagent **13** (214 mg, 0.524 mmol) with 0.4 mL dry THF was added and the resulting mixture was stirred at –95 ℃ for 20 min. The resulting mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 100:1) to yield **12a** (45.0 mg, 63%, *E*/*Z* = 8.5:1) as a light yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz, *E* isomer) δ 6.91 (d, *J* = 8.2 Hz, 1H), 6.77 (s, 1H), 6.74 (s, 1H), 6.48 (d, *J* = 7.9 Hz, 1H), 4.57 (q, *J* = 5.0 Hz, 2H), 0.97 (s, 9H), 0.96 (s, 9H), 0.19 (s, 6H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 147.9, 147.2, 135.0, 124.7, 122.3, 121.9, 121.4, 120.1, 119.5, 67.2 (q, 1C, J_{CF} = 154.1 Hz, CH_2CF_3), 25.9, 25.8, 18.5, 18.4, –4.0, –4.1; IR υ_{max} (neat, cm^{-1}) 2936, 2864, 1513, 1423, 1298, 1205, 835; HRMS (FAB) calcd for $C_{22}H_{38}F_3O_6SSi_2$ 543.1880 ($[M+H]^+$), found 543.1878.

(*Z*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)styryl (2,2,2-trichloroethyl) sulfate (12b)



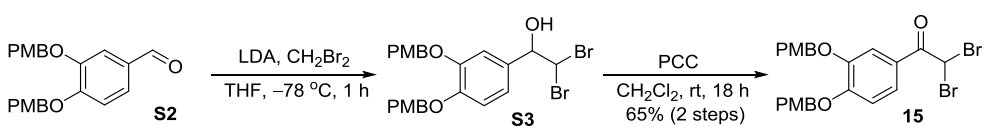
To a solution of the aldehyde **11** (985 mg, 2.60mol) in dry THF (12 mL) was cooled to –90 ℃ (cooling bath with using liquid nitrogen and CH_3OH) followed by the addition of 1,8-diazabicycloundec-7-ene (0.777 mL, 5.20 mmol). The reaction mixture was stirred at –90 ℃ for 20 min. Then sulfuryl reagent **13** (4.24g, 10.4 mmol) with 3 mL dry THF was added. The resulting mixture was stirred at –90 ℃ for 10 min, and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 100:1) to yield **12b** (1.30 g, 92%, *E*/*Z* = 1:6) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, *Z* isomer) δ 7.09 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.81–6.74 (m, 1H), 6.55 (d, *J* = 6.5 Hz, 1H), 5.83 (d, *J* = 6.5 Hz, 1H), 4.44 (q, *J* = 7.6 Hz, 2H), 0.97–0.96 (m, 18H), 0.23–0.17 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz,) δ 147.6, 146.9, 132.6, 124.8, 123.0, 121.9, 121.8, 121.0, 119.3, 117.0, 67.2 (q, 1C, J_{CF} = 154.5 Hz, CH_2CF_3), 25.8, 18.4, 13.0, –4.0; IR υ_{max} (neat, cm^{-1}) 2933, 2861, 1509, 1265, 1203, 835; HRMS (FAB) calcd for $C_{22}H_{38}F_3O_6SSi_2$ 543.1880 ($[M+H]^+$), found 543.1883.

(*E*)-3,4-dihydroxystyryl (2,2,2-trifluoroethyl) sulfate (14)



The solution of tetra-*n*-butylammonium fluoride in THF (1.0 M, 1.11 mL, 1.11 mmol) was added to a solution of **12a** (300 mg, 0.553 mmol) in THF (5.5 mL). The reaction mixture was stirred at rt for 10 min. The resulting mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/EtOAc, 2:1) afforded **14** (170 mg, 99%) as a yellow oil; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.07 (d, J = 12.1 Hz, 1H), 6.81 (s, 1H), 6.72 (s, 2H), 6.57 (d, J = 12.1 Hz, 1H), 4.91 (q, J = 8.1 Hz, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 148.3, 147.5, 136.7, 125.7, 124.7, 121.2, 117.4, 115.0, 69.3 (q, 1C, J_{CF} = 151.3 Hz, CH_2CF_3); IR (neat, cm^{-1}) υ_{max} 2973, 1420, 1295, 1170, 1001, 875, 815; HRMS (FAB) calcd for $C_{10}H_9F_3O_6S$ 314.0072 (M^+), found 314.0063.

1-(3,4-bis((4-methoxybenzyl)oxy)phenyl)-2,2-dibromoethan-1-one (15)

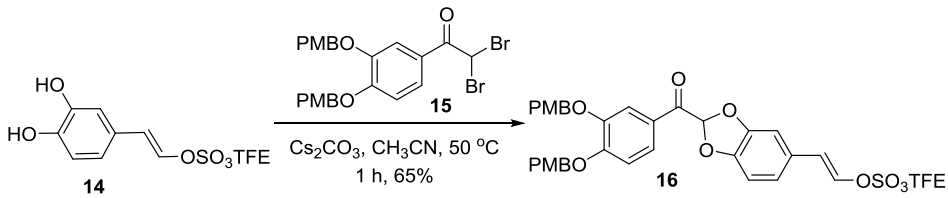


Dibromomethane (2.70 mL, 38.5 mmol) was added to a solution of 3,4-bis((4-methoxybenzyl)oxy)benzaldehyde **S2**[20] (4.90 g, 12.9 mmol) in dry THF (42 mL).

The reaction mixture was stirred for 30 min prior to cooling to −78 ℃ and a solution of lithium diisopropylamide in THF (2.0 M, 23 mL, 45.2 mmol) was added during the course of 10 min. After stirring at −78 ℃ for 1 h, the reaction was quenched with water. Then, the resulting mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue **S3** was used in the next reaction without further purification.

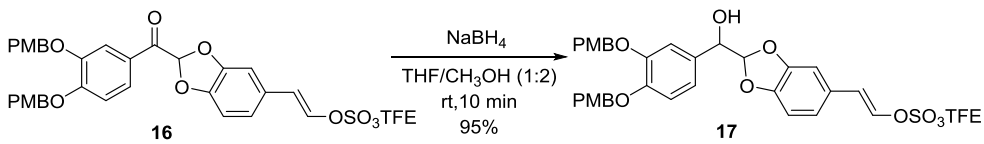
To a solution of the above residue **S3** in CH_2Cl_2 (60 mL) at rt, PCC (56.0 g, 26.0 mmol) was added. The resulting mixture was stirred for 18 h, and then filtered using a silica gel filter and washed with CH_2Cl_2. The filtrates were concentrated *in vacuo*. The residue was purified by recrystallization (hexane/CH_2Cl_2) to afford **15** (4.61 g, 65% for two steps) as a yellow solid; m.p. 122–124 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66–7.62 (m, 2H), 7.36 (t, J = 8.8 Hz, 5H), 6.94 (d, J = 8.3 Hz, 1H), 6.89–6.86 (m, 5H), 6.59 (s, 1H), 5.15 (s, 2H), 5.10 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.5, 159.5, 159.4, 154.4, 148.7, 129.1, 128.8, 128.4, 128.0, 124.6, 123.4, 115.5, 114.0, 113.9, 112.8, 71.0, 70.6, 55.2, 39.6; IR (neat, cm^{-1}) υ_{max} 2931, 1688, 1514, 1241, 1160, 983, 821; HRMS (FAB) calcd for $C_{24}H_{23}Br_2O_5$ 548.9912 ($[M+H]^+$), found 548.9905.

(*E*)-2-(2-(3,4-bis((4-methoxybenzyl)oxy)benzoyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (16)



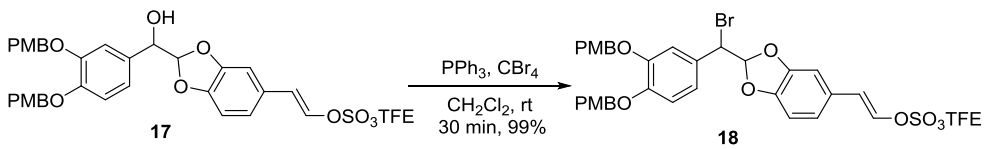
A solution of **14** (286 mg, 0.910 mmol), Cs_2CO_3 (621 mg, 1.91 mmol), and **15** (500 mg, 0.910 mmol) in CH_3CN (6 mL) was stirred at 50 ℃ for 1 h. The resulting mixture was filtered using celite. Then the resulting residue was evaporated and purified by silica gel column chromatography (hexane/EtOAc, 3:1) to afford **16** (415 mg, 65%) as a yellow gum; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63–7.61 (m, 2H), 7.33 (dd, *J* = 8.5, 1.8 Hz, 4H), 6.97 (d, *J* = 3.9 Hz, 1H), 6.95 (s, 1H), 6.89–6.84 (m, 7H), 6.82 (s, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.52 (d, *J* = 12.1 Hz, 1H), 5.16 (s, 2H), 5.08 (s, 2H), 4.57 (q, *J* = 7.7 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.2, 159.5, 159.4, 154.5, 148.8, 147.6, 147.5, 135.4, 129.1, 128.8, 128.5, 128.0, 126.0, 125.9, 124.5, 122.0, 121.6, 114.6, 114.0, 113.9, 113.0, 109.0, 106.3, 105.6, 70.9, 70.6, 67.3 (q, 1C, J_{CF} = 154.0 Hz, CH_2CF_3), 55.3, 55.2; IR (neat, cm^{-1}) υ_{max} 2936, 1689, 1589, 1514, 1420, 1241, 991, 821; HRMS (FAB) calcd for $C_{34}H_{30}F_3O_{11}S$ 703.1461 ($[M+H]^+$), found 703.1468.

(*E*)-2-(2-((3,4-bis((4-methoxybenzyl)oxy)phenyl)(hydroxy)methyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (17)



To a solution of **16** (400 mg, 0.570 mmol) in THF (2 mL) at rt, CH_3OH (4 mL) and $NaBH_4$ (22.0 mg, 0.570 mmol) were added. The mixture was stirred at rt for 10 min. The resulting mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/EtOAc, 2:1) afforded **17** as a yellow gum (381 mg, 95%, 1:1 dr); ^{1}H NMR ($CDCl_3$, 500 MHz; two diastereomers in a 1:1 ratio) δ 7.33 (t, *J* = 6.1 Hz, 4H), 7.05 (d, *J* = 3.6 Hz, 1H), 6.96 (d, *J* = 12.1 Hz, 1H), 6.93 (s, 2H), 6.87 (d, *J* = 8.4 Hz, 4H), 6.75–6.69 (m, 3H), 6.51 (d, *J* = 12.1 Hz, 1H), 6.11 (t, *J* = 4.4 Hz, 1H), 5.02 (s, 2H), 5.06 (s, 2H), 4.78 (q, *J* = 4.4 Hz, 1H), 4.57 (q, *J* = 7.6 Hz, 2H), 3.79 (s, 6H), 2.35 (t, *J* = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz; diastereomer 1/diastereomer 2) δ 159.3, 149.5, 149.1/149.0, 148.3/148.2, 148.1/148.0, 135.2, 130.0/129.9, 129.2/129.1, 128.9, 125.5/125.4, 121.8, 121.7/121.6, 120.4/120.3, 115.0/114.9, 114.4/114.3, 114.1/114.0, 113.8, 112.2/112.1, 108.6/108.4, 105.8/105.7, 74.0/73.9, 71.2/71.0, 67.3 (q, 1C, *J* = 154.1 Hz, CH_2CF_3), 55.2; IR (neat, cm^{-1}) υ_{max} 3500, 1610, 1513, 1419, 1203, 1172, 1021, 820; HRMS (FAB) calcd for $C_{34}H_{31}F_3O_{11}S$ 704.1539 (M^+), found 704.1548.

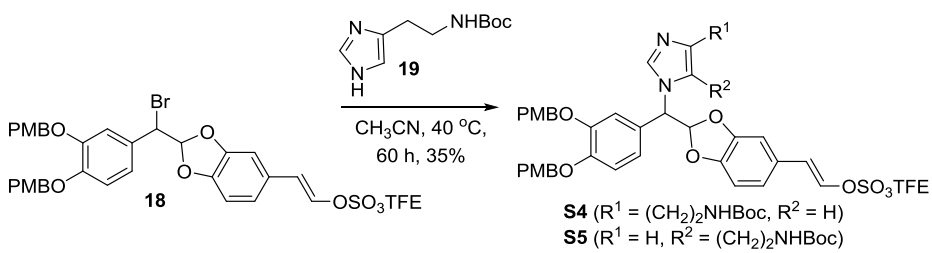
(*E*)-2-(2-((3,4-bis((4-methoxybenzyl)oxy)phenyl)bromomethyl)benzo[*d*][1,3] dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (18)



To a solution of **17** (350 mg, 0.497 mmol) in dry CH_2Cl_2 (15 mL) at rt, PPh_3 (262 mg, 1.00 mmol) and CBr_4 (331 mg, 1.00 mmol) were added. The mixture was stirred at rt for 30 min. The resulting mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to yield **18** (379 mg, 99%, 1:1 dr) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz; two diastereomers in a 1:1 ratio) δ 7.32 (t, *J* = 9.4 Hz, 1H), 7.09 (dd, *J* = 3.8, 2.1Hz, 1H), 6.95 (dd, *J* = 12.1, 8.7 Hz, 1H), 6.88–6.84 (m, 5H), 6.76–6.67 (m, 3H), 6.49 (dd, *J* = 12.1, 2.8 Hz, 1H), 6.36 (d, *J* = 4.1 Hz, 1H), 5.04 (s, 4H), 4.57 (dq, *J* = 7.6, 3.1 Hz, 2H), 3.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz; diastereomer 1/diastereomer 2) δ 159.3, 149.9, 148.9/148.8, 148.1, 148.0/147.9, 135.3, 129.3/129.2, 128.9, 127.9, 125.6, 122.3, 121.8/121.7, 116.2, 114.4/114.3, 113.9/113.8, 110.8/110.7, 108.5/108.4, 105.7/105.6, 71.3/70.8, 67.3 (q, 1C, *J* = 154.0 Hz, CH_2CF_3), 55.2, 52.8; IR (neat, cm^{-1}) υ_{max} 3510, 2922, 1611, 1497, 1204, 1023, 821; HRMS (FAB) calcd for $C_{34}H_{30}BrF_3O_{10}S$ 766.0695 (M^+), found 766.0692.

((*E*)-2-(2-((3,4-bis((4-methoxybenzyl)oxy)phenyl)(4-(2-((*tert*-butoxycarbonyl) amino)ethyl)-1H-imidazol-1-yl)methyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (S4)

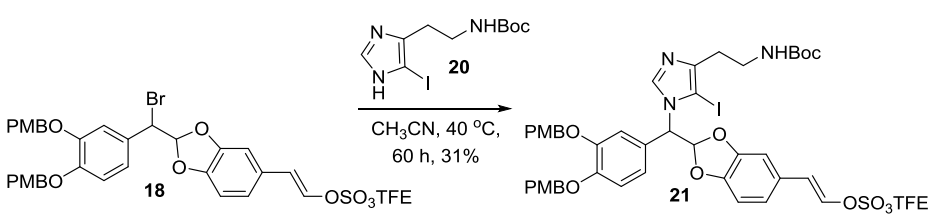
(*E*)-2-(2-((3,4-bis((4-methoxybenzyl)oxy)phenyl)(5-(2-((*tert*-butoxycarbonyl) amino)ethyl)-1H-imidazol-1-yl)methyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (S5)



A solution of **18** (32.0 mg, 0.0417 mmol) and **19** (26.0 mg, 0.123 mmol) in dry CH_3CN (1 mL) was stirred at 40 ℃ for 60 h. The resulting mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 1:3) to yield mixture **S4** and **S5** (12.7 mg, 35%, two tautomers in a 1:1 ratio) as a yellow gum; ^{1}H NMR ($CDCl_3$, 500 MHz; two tautomers in a 1:1 ratio) δ 7.32–7.27 (m, 4H), 6.96–6.83 (m, 8H), 6.68–6.58 (m, 3H), 6.47–6.42 (m, 1H), 5.06–4.99 (m, 2H), 4.60–4.54 (m, 2H), 3.99–3.96 (m, 1H), 3.79 (s, 6H), 3.62–3.58 (m, 1H), 3.24–3.17

(m, 1H), 2.64–2.58 (m, 1H), 1.41–1.36 (m, 9H); ^{13}C NMR ($CDCl_3$, 200 MHz; tautomer 1/tautomer 2) δ 159.4/159.3, 135.5, 129.2/129.1, 128.9/128.8, 125.9/125.8, 121.9/121.5, 121.7, 121.5/121.4, 115.9, 114.8, 113.9/113.8, 108.6/108.4, 105.8, 71.0/70.9, 67.3 (q, 1C, J = 154.0 Hz, CH_2CF_3), 65.6, 62.8, 55.2, 29.6, 28.4/28.3; IR (neat, cm^{-1}) υ_{max} 2935, 1716, 1476, 1129, 1045, 767; HRMS (FAB) calcd for $C_{44}H_{47}F_3N_3O_{12}S$ 898.2827 ($[M+H]^+$), found 898.2833.

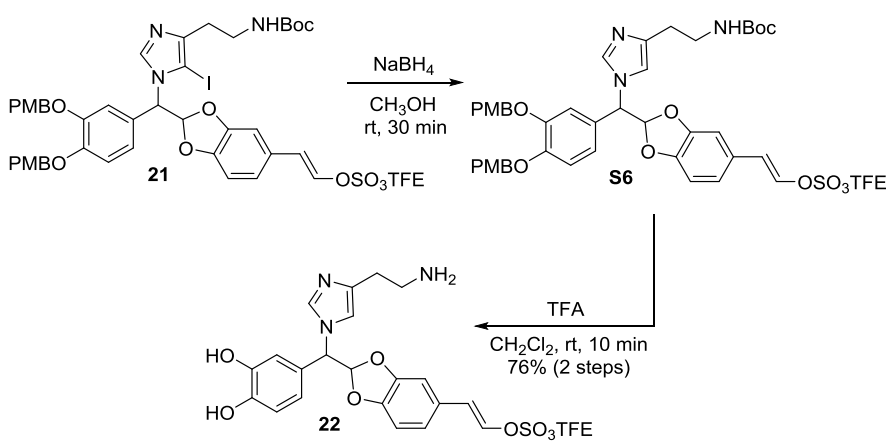
(*E*)-2-(2-((3,4-bis((4-methoxybenzyl)oxy)phenyl)(4-(2-((*tert*-butoxycarbonyl) amino)ethyl)-5-iodo-1H-imidazol-1-yl)methyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (21)



A solution of **18** (340 mg, 0.443 mmol) and **20** (597 mg, 1.76 mmol) in dry CH_3CN (6 mL) was stirred at 40 ℃ for 60 h. The resulting mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 1:1) to yield diastereomeric mixture **21** {140 mg, 31% (81% brsm), 1:1 dr} as a yellow gum; ^{1}H NMR ($CDCl_3$, 500 MHz; two diastereomers in a 1:1 ratio) δ 7.69 (s, 1H), 7.29 (dd,

J = 11.7, 8.6 Hz, 4H), 6.94 (dd, *J* = 12.0, 4.7 Hz, 1H), 6.87–6.85 (m, 7H), 6.70–6.64 (m, 4H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.45 (d, *J* = 12.1 Hz, 1H), 5.48 (s, 1H), 5.03 (s, 2H), 5.01 (s, 2H), 4.57 (q, *J* = 7.6 Hz, 2H), 3.79 (s, 6H), 3.27 (br s, 2H), 2.63 (br s, 2H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz; diastereomer 1/ diastereomer 2) δ 159.4, 155.8, 149.9, 148.9, 147.4, 147.3/147.2, 139.1, 135.5, 129.1/128.9, 128.8/128.7, 125.9/125.8, 125.5, 121.9/121.8, 121.7, 121.5/121.4, 116.1/116.0, 114.7, 113.9, 109.4, 108.7/108.4, 105.8/105.6, 71.5/71.4, 70.8, 67.3 (q, 1C, *J* = 154.0 Hz, CH_2CF_3), 63.4, 55.2, 39.7, 28.4; IR (neat, cm^{-1}) υ_{max} 2924, 1702, 1513, 1244, 1170, 1022, 754; HRMS (FAB) calcd for $C_{44}H_{46}F_3N_3O_{12}S$ 1024.1799 ($[M+H]^+$), found 1024.1797.

(*E*)-2-(2-((4-(2-aminoethyl)-1H-imidazol-1-yl)(3,4-dihydroxyphenyl)methyl) benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (22)



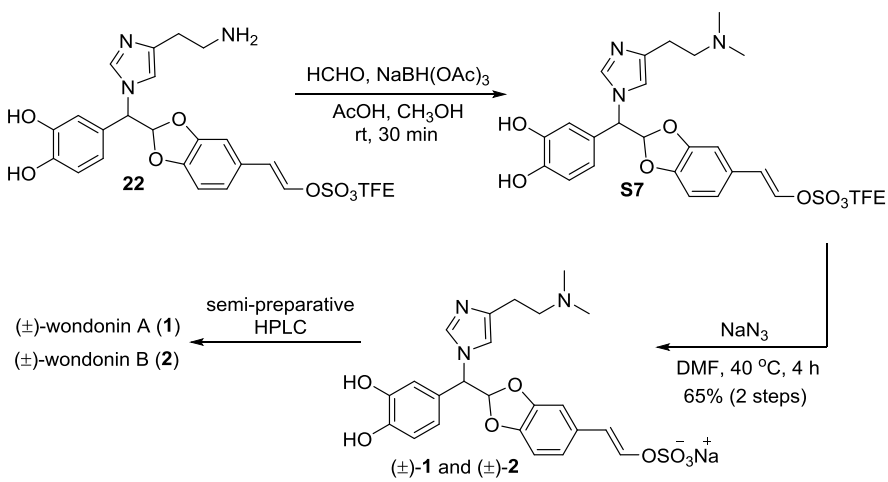
To a solution of **21** (131 mg, 0.128 mmol) in CH_3OH (1.2 mL) at rt, $NaBH_4$ (48.0

mg, 1.28 mmol) was slowly added. The mixture was stirred at rt for 10 min, and $NaBH_4$ (48.0 mg, 1.28 mmol) was slowly added again. The mixture was stirred at rt for 20 min. The resulting mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by short silica gel filter to yield **S6** (94.0 mg) as a yellow gum;

To a solution of **S6** (94.0 mg) in CH_2Cl_2 (1.4 mL) at rt, TFA (0.7 mL) was added. The reaction mixture was stirred at rt for 10 min. Then, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was washed with CH_2Cl_2 for three times to yield **22** (76.0 mg, 76% for two steps) as a brown gum; ^{1}H NMR (CD_3OD, 600 MHz) δ 7.94 (d, *J* = 5.5 Hz, 1H), 7.17 (dd, *J* = 11.9, 2.7 Hz 1H), 7.14–6.76 (m, 9H), 6.61 (dd, *J* =11.9, 5.5 Hz 1H), 5.70 (d, *J* = 8.7 Hz, 1H), 4.91 (dq, *J* = 8.1, 2.3 Hz, 2H), 3.03 (td, *J* = 7.6, 1.7 Hz, 2H), 2.78 (td, *J* = 10.7, 3.7 Hz, 2H); ^{13}C NMR (CD_3OD, 150 MHz, diastereomer 1/diastereomer 2) δ 149.9/149.8, 149.7/149.6, 148.3, 147.8/147.7, 139.7/139.6, 138.0/137.9, 131.1/131.0, 128.5/128.3, 126.6, 124.0/123.9, 122.3/122.2, 119.9/119.8, 117.7/117.4, 115.6, 111.8, 107.7/107.6, 69.3 (q, 1C, *J* = 157.8 Hz, CH_2CF_3), 41.0/40.9, 26.7/26.6; IR (neat, cm^{-1}) υ_{max} 3110, 1685, 1502, 1471, 1280, 1043; HRMS (FAB) calcd for $C_{23}H_{23}F_3N_3O_8S$ 558.1163

([M+H]$^+$), found 558.1152.

(±)-Wondonin A (1) and (±)-wondonin B (2)



To a solution of **22** (50.0 mg, 0.0896 mmol) in CH_3OH/AcOH (1.1 mL/0.038 mL) at rt, HCHO 37% wt. in water (0.122 mL, 0.897 mmol) and $NaBH(OAc)_3$ (110 mg, 0.519 mmol) were added. The reaction mixture was stirred at rt for 30 min. Then, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield crude product **S7** (40.0 mg) as a brown gum;

To a solution of the above crude product **S7** (40.0 mg, 0.0683 mmol) in DMF (0.5 mL), NaN_3 (9.00 mg, 0.137 mmol) was added. The mixture was stirred at 40 ℃ for 4 h. Then the solvent was evaporated, and the resulting residue was purified by Sephadex LH20 column chromatography (Water/CH_3OH, 4:1) to yield mixture of

diastereomers (**1** and **2**) (26.0 mg, 65% for two steps) as a brown gum;

The mixture of diastereomers (**1** and **2**) was separated by C18 reversed-phase semi-preparative HPLC (phenomenex luna 10μ column, 1cm × 25 cm; 30% to 70% CH_3OH in water containing 0.1% HCOOH) to afford (±)-wondonin A (**1**, 5.2 mg) as a brown gum and afford (±)-wondonin B (**2**, 6.1 mg) as a brown gum;

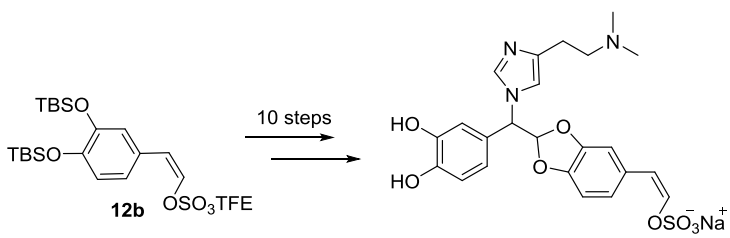
(±)-wondonin A (**1**): ^{1}H NMR (CD_3OD, 500 MHz) δ 7.62 (s, 1H), 7.14 (d, *J* = 12.5 Hz, 1H), 7.02 (d, *J* = 1.8 Hz, 1H), 6.92–6.91 (m, 2H), 6.82–6.79 (m, 3H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.11 (d, *J* = 12.5 Hz, 1H), 5.59 (s, 1H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.79–2.74 (m, 2H), 2.72 (s, 6H); ^{13}C NMR (CD_3OD, 150 MHz) δ 149.8, 148.3, 148.1, 147.7, 140.8, 140.2, 138.7, 131.1, 127.3, 122.2, 122.1, 119.3, 117.7, 117.4, 116.2, 111.7, 109.8, 106.7, 65.2, 60.0, 44.8, 25.3; IR (neat, cm^{-1}) υ_{max} 3480, 1654, 1501, 1237, 1027; HRMS (Q-TOF) calcd for $C_{23}H_{24}N_3O_8S$ 502.1290 ($[M-Na]^-$), found 502.1304.

(±)-wondonin B (**2**): ^{1}H NMR (CD_3OD, 500 MHz) δ 7.56 (s, 1H), 7.13 (d, *J* = 12.5 Hz, 1H), 7.00 (s, 1H), 6.90 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 2H), 6.73 (s, 1H), 6.65 (s, 2H), 6.09 (d, *J* = 12.5 Hz, 1H), 5.59 (s, 2H), 2.90 (t, *J* = 7.1 Hz, 2H), 2.74 (q, *J* = 7.5 Hz, 2H), 2.66 (s, 6H); ^{13}C NMR (CD_3OD, 125 MHz) δ 149.7, 148.4, 148.1, 147.6, 140.9, 139.9, 138.5, 131.3, 127.2, 122.2, 121.8, 119.7, 117.7, 117.4, 116.1, 111.7, 109.9, 106.7, 65.1, 60.0, 44.8, 25.5; IR (neat, cm^{-1}) υ_{max} 3410, 1645, 1491, 1247, 1020; HRMS (Q-TOF) calcd for $C_{23}H_{24}N_3O_8S$ 502.1290

([M-Na]$^-$), found 502.1300.

IV-2. Synthesis of (±)-isowondonin A (3) and (±)-isowondonin B (4)

(±)-Isowondonin A (3) and (±)-isowondonin B (4)



(±)-isowondonin A (**3**) and (±)-isowondonin B (**4**)

Following the same procedure of as that for the synthesis of (±)-wondonin A (**1**) and (±)-wondonin B (**2**), starting from compound **12b** (300 mg, 0.552 mmol), 1.40 mg of the corresponding (±)-isowondonin A (**3**) as a brown gum and 1.20 mg of (±)-isowondonin B (**4**) as a brown gum were obtained from 10 steps (total yield = 0.9%);

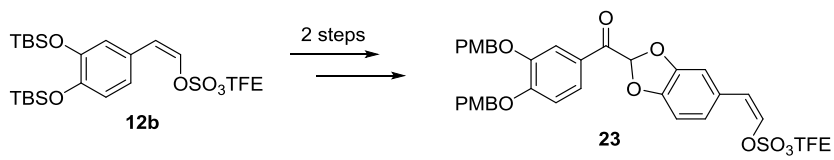
(±)-isowondonin A (**3**): ^{1}H NMR (CD_3OD, 500 MHz) δ 7.62 (s, 1H), 7.31 (d, *J* = 1.2 Hz, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 6.95–6.93 (m, 2H), 6.83–6.81 (m, 2H), 6.75 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.63 (d, *J* = 7.0 Hz, 1H), 6,59 (d, *J* = 8.0 Hz, 1H), 5.58 (s, 1H), 5.46 (d, *J* = 7.0 Hz, 1H), 2.92–2.91 (m, 2H), 2.78–2.73 (m, 2H), 2.71 (s, 6H);

(±)-isowondonin B (**4**): ^{1}H NMR (CD_3OD, 600 MHz) δ 7.51 (s, 1H), 7.15 (d, *J* =

1.3 Hz, 1H), 7.03 (s, 2H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 5.1, 3.2 Hz, 2H), 6.65 (t, *J* = 7.8 Hz, 2H), 5.61 (s, 1H), 5.43(d, *J* = 7.1 Hz, 1H), 2.94 (t, *J* = 7.1, 2H), 2.787–2.73 (m, 2H), 2.70 (s, 6H).

IV-3. Synthesis of (–)-isowondonin A (3) and (–)-isowondonin B (4)

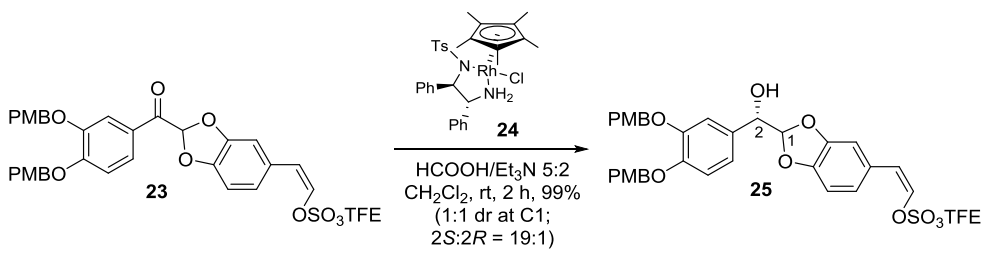
(*Z*)-2-(2-(3,4-bis((4-methoxybenzyl)oxy)benzoyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (23)



Following the same procedure as that for the synthesis of **16**, starting from compound **12b** (495 mg, 0.912 mmol), the corresponding compound **23** (397 mg, 58% for two steps) was obtained as a yellow gum; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65–7.61 (m, 2H), 7.35–7.32 (m, 4H), 7.15 (d, *J* = 1.4 Hz, 1H), 6.96 (dd, *J* = 8.7, 2.2 Hz, 2H), 6.89–6.85 (m, 6H), 6.58 (d, *J* = 6.6 Hz, 1H), 5.85 (d, *J* = 6.6 Hz, 1H), 5.16 (s, 2H), 5.08 (s, 2H), 4.47 (dq, *J* = 7.6, 1.6 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.1, 159.4, 159.3, 154.5, 148.8, 147.2, 147.1, 133.1, 129.1, 128.8, 128.4, 128.0, 125.9, 124.6, 124.4, 116.5, 114.5, 114.0, 113.9, 112.9, 109.4, 108.8, 105.5, 70.9, 70.6, 67.4 (q, 1C, *J* = 157.0 Hz, CH_2CF_3), 55.2; IR

(neat, cm^{-1}) υ_{max} 2839, 1691, 1591, 1514, 1424, 1244, 992, 814; HRMS (FAB) calcd for $C_{34}H_{30}F_3O_{11}S$ 703.1461 ($[M+H]^+$), found 703.1465.

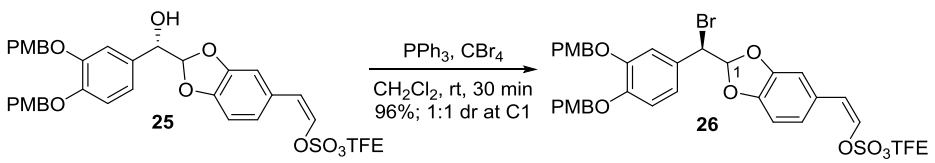
(*Z*)-2-(2-((*S*)-(3,4-bis((4-methoxybenzyl)oxy)phenyl)(hydroxy)methyl)benzo[*d*] [1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (25)



To a solution of **23** (580 mg, 0.825 mmol) in CH_2Cl_2 (6 mL) at rt, **24** (10.5 mg, 0.0160 mmol) and HCOOH/Et_3N = 5:2 (0.25 mL) were added. The mixture was stirred at rt for 2 h. The mixture was evaporated and purified by silica gel column chromatography (hexane/EtOAc, 2:1) to yield **25** (575 mg, 99%, 1:1 dr at C1) as a yellow oil; The absolute configuration at C2 was assigned as *S* with an *S*/*R* ratio of 19/1 by Mosher analysis; ^{1}H NMR ($CDCl_3$, 400 MHz; two diastereomers in a 1:1 ratio) δ 7.35–7.31 (m, 4H), 7.06–6.85 (m, 10H), 6.75 (dd, *J* = 17.2, 8.1 Hz, 1H), 6.57 (dd, *J* = 6.5, 2.0 Hz, 1H), 6.12 (d, *J* = 4.5 Hz, 1H), 5.84 (dd, *J* = 6.6, 1.8 Hz, 1H), 5.06 (s, 2H), 5.05 (s, 2H), 4.80 (t, *J* = 3.1 Hz, 1H), 4.45 (dq, *J* = 7.6, 4.9 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz; diastereomer 1/diastereomer 2) δ 159.3, 149.5/149.4, 149.1/149.0, 148.0/147.9, 147.8/147.7,

132.9, 130.0, 129.2/129.1, 128.9, 125.5/125.4, 124.0, 122.6, 121.8, 120.4/120.3, 119.8, 116.7, 114.9, 114.3/114.0, 113.8, 112.1, 109.0/108.9, 108.3/108.2, 73.8, 71.2/71.0, 67.3 (q, 1C, J = 154.4 Hz, CH_2CF_3), 55.2; IR (neat, cm^{-1}) υ_{max} 3507, 1612, 1513, 1425, 1201, 1166, 1034, 817; HRMS (FAB) calcd for $C_{34}H_{31}F_3O_{11}S$ 704.1539 (M^+), found 704.1535.

(*Z*)-2-(2-((*R*)-(3,4-bis((4-methoxybenzyl)oxy)phenyl)bromomethyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (26)

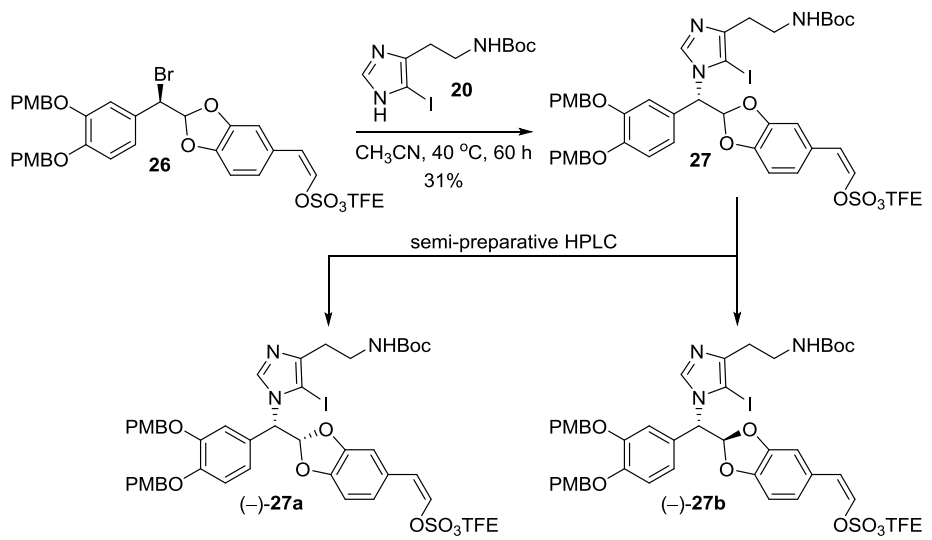


Following the same procedure as that for the synthesis of **18**, starting from compound **25** (560 mg, 0.795 mmol), the corresponding compound **26** (590 mg, 96%; 1:1 dr at C1) was obtained as a yellow gum; ^1H NMR ($CDCl_3$, 400 MHz; two diastereomers in a 1:1 ratio) δ 7.32 (dd, J = 10.6, 8.3 Hz, 4H), 7.10–6.69 (m, 11H), 6.56 (dd, J = 6.5, 4.5 Hz, 1H), 6.38 (d, J = 4.2 Hz, 1H), 5.83 (dd, J = 6.6, 2.5 Hz, 1H), 5.04 (s, 4H), 4.50–4.42 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz; diastereomer 1/diastereomer 2) δ 159.3, 149.9, 148.8/148.7, 147.7/147.6, 147.5, 132.9, 129.2, 128.8, 127.9, 125.6/125.5, 124.1, 122.3, 116.6, 116.0, 114.3, 113.9/113.8, 110.7, 108.9/108.8, 108.3/108.2, 71.3/70.8, 67.3 (q, 1C, J = 160.0 Hz, CH_2CF_3), 55.2, 52.8; IR (neat, cm^{-1}) υ_{max} 3512, 2924, 1610, 1499, 1202, 1036, 815;

HRMS (FAB) calcd for $C_{34}H_{30}BrF_3O_{10}S$ 766.0695 (M^+), found 766.0685.

(*Z*)-2-((*R*)-2-((*S*)-(3,4-bis((4-methoxybenzyl)oxy)phenyl)(4-(2-((*tert*-butoxy carbonyl)amino)ethyl)-5-iodo-1H-imidazol-1-yl)methyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (–)-27a

(*Z*)-2-((*S*)-2-((*S*)-(3,4-bis((4-methoxybenzyl)oxy)phenyl)(4-(2-((*tert*-butoxy carbonyl)amino)ethyl)-5-iodo-1H-imidazol-1-yl)methyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (–)-27b



Following the same procedure as that for the synthesis of **21**, starting from compound **26** (212 mg, 0.276 mmol), the corresponding compound **27** (86.0 mg, 31%; 1:1 dr at C1) was obtained as a yellow gum, Then, two diastereomers (86.0

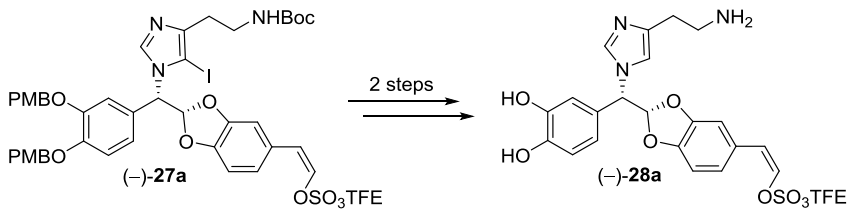
mg) were separated by C18 reversed-phase semipreparative HPLC (phenomenex luna 10μ column, 1cm×25 cm, 80% aqueous CH_3OH in water containing 0.1% HCOOH) to yield (–)-**27a** (25.0 mg), (–)-**27b** (20.0 mg) and mixture of two diastereomers (41 mg).

(–)-**27a**: $[\alpha]^{20}_D$ –34.1 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.68 (s, 1H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 1.1 Hz, 1H), 6.89–6.83 (m, 8H), 6.69–6.66 (m, 2H), 6.55 (d, *J* = 6.6 Hz, 1H), 5.79 (d, *J* = 6.6 Hz, 1H), 5.49 (d, *J* = 2.7 Hz, 1H), 5.03 (s, 2H), 5.01 (s, 2H), 4.94 (br s, 1H), 4.50 (q, *J* = 7.6 Hz, 2H), 3.79 (s, 6H), 3.31–3.26 (m, 2H), 2.62 (q, *J* = 5.6 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 159.4, 155.8, 149.9, 148.8, 147.1, 146.9, 139.2, 133.1, 129.2, 128.9, 128.8, 125.8, 125.7, 124.2, 121.8, 116.4, 116.1, 114.8, 113.9, 109.5, 108.9, 108.5, 71.5, 70.9, 67.3 (q, 1C, *J* = 158.9 Hz, CH_2CF_3), 55.2, 28.7; IR (neat, cm^{-1}) υ_{max} 2935, 1703, 1497, 1245, 1172, 996, 751; HRMS (FAB) calcd for $C_{44}H_{46}F_3N_3O_{12}S$ 1024.1799 ($[M+H]^+$), found 1024.1801.

(–)-**27b**: $[\alpha]^{20}_D$ –29.5 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69 (s, 1H), 7.28 (dd, *J* = 11.4, 8.5 Hz, 4H), 6.95 (s, 1H), 6.88–6.84 (m, 8H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 2.8 Hz, 1H), 6.55 (d, *J* = 6.6 Hz, 1H), 5.80 (d, *J* = 6.6 Hz, 1H), 5.48 (d, *J* = 2.7 Hz, 1H), 5.03 (s, 2H), 5.01 (s, 2H), 4.48 (q, *J* = 7.6 Hz, 2H), 3.79 (s, 6H), 3.28–3.27 (m, 2H), 2.62 (t, *J* = 6.2 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.4, 155.8, 149.9, 148.8, 147.1, 146.9, 139.0, 133.1, 129.1, 128.9,

128.8, 125.8, 125.7, 124.2, 121.7, 116.4, 116.1, 114.8, 113.9, 109.4, 108.9, 108.5, 71.5, 70.9, 67.3 (q, 1C, J = 154.0 Hz, CH_2CF_3), 55.2, 29.6, 28.4; IR (neat, cm^{-1}) υ_{max} 2935, 1703, 1497, 1245, 1176, 996, 751; HRMS (FAB) calcd for $C_{44}H_{46}F_3N_3O_{12}S$ 1024.1799 ($[M+H]^+$), found 1024.1808.

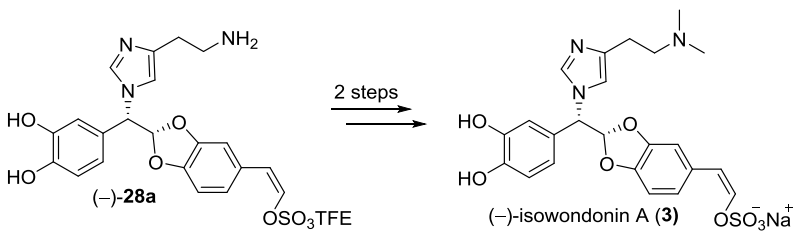
(*Z*)-2-((*S*)-2-((*S*)-(4-(2-aminoethyl)-1H-imidazol-1-yl)(3,4-dihydroxyphenyl) methyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (–)-28a



Following the same procedure as that for the synthesis of **22**, starting from compound (–)-**27a** (25.0 mg, 0.024 mmol), the corresponding compound (–)-**28a** (10.4 mg, 74% for two steps) was obtained as a yellow gum; $[\alpha]^{20}_D$ –8.7 (*c* 0.45, CH_3OH); ^1H NMR (CD_3OD, 800 MHz) δ 8.25 (s, 1H), 7.27 (s, 1H), 7.10 (d, J = 1.5 Hz, 1H), 7.04 (d, J = 2.1 Hz, 1H), 6.97 (dd, J = 8.1, 1.5 Hz, 1H), 6.93 (td, J = 8.3, 2.0 Hz, 2H), 6.88 (d, J = 3.1 Hz, 1H), 6.82 (d, J = 8.2 Hz, 2H), 6.78 (d, J = 8.1 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 5.96 (d, J = 6.6 Hz, 1H), 5.79 (d, J = 2.9 Hz, 1H), 4.94–4.92 (m, 2H), 3.07 (t, J = 7.4 Hz, 2H), 2.88 (t, J = 7.3 Hz, 2H); ^{13}C NMR (CD_3OD, 200 MHz) δ 149.5, 149.4, 148.6, 147.8, 139.1, 135.5, 135.4, 128.4, 126.3, 125.9, 124.8, 123.9, 122.5, 122.4, 120.5, 118.2, 117.8 ,117.5, 111.6, 110.8, 110.5,

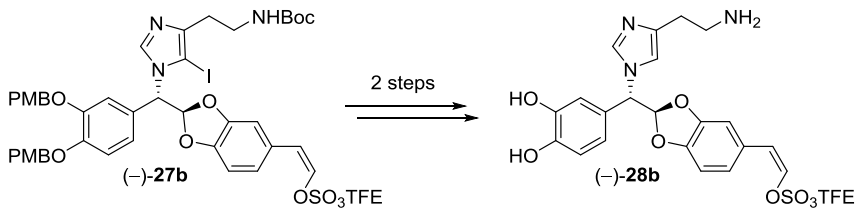
110.2, 69.6 (q, 1C, J = 151.7 Hz, CH_2CF_3), 66.0, 40.7, 25.9; IR (neat, cm^{-1}) υ_{max} 3125, 1682, 1502, 1423, 1278, 1044; HRMS (FAB) calcd for $C_{23}H_{23}F_3N_3O_8S$ 558.1163 ($[M+H]^+$), found 558.1165.

(–)-Isowondonin A (3)



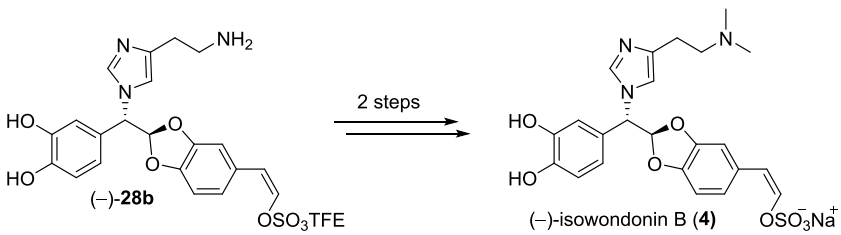
Following the same procedure as that for the synthesis of (±)-wondonin A (**1**) and (±)-wondonin B (**2**), starting from compound (–)-**28a** (10.4 mg, 0.0186 mmol), the corresponding compound (–)-isowondonin A (**3**) 6.5 mg, 67% for two steps) was obtained as a yellow gum; $[\alpha]^{20}_D$ –4.2 (*c* 0.72, CH_3OH); ^1H NMR (CD_3OD, 600 MHz) δ 7.62 (s, 1H), 7.31 (d, J = 1.2 Hz, 1H), 7.07 (d, J = 1.6 Hz, 1H), 6.95–6.94 (m, 2H), 6.83–6.81 (m, 2H), 6.75 (dd, J = 8.1, 1.0 Hz, 1H), 6.64 (d, J = 7.0 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 5.58 (s, 1H), 5.46 (d, J = 7.0 Hz, 1H), 2.92–2.91 (m, 2H), 2.78–2.73 (m, 2H), 2.71 (s, 6H); ^{13}C NMR (CD_3OD, 150 MHz) δ 149.3, 148.2, 147.8, 147.7, 140.5, 138.7, 137.8, 130.8, 127.2, 124.6, 122.4, 119.6, 117.7, 117.4, 111.8, 111.6, 110.5, 109.3, 65.3, 59.4, 44.4, 24.8; IR (neat, cm^{-1}) υ_{max} 3460 (br), 2945, 1543, 1510, 1275, 1124, 1017; HRMS (Q-TOF) calcd for $C_{23}H_{24}N_3O_8S$ 502.1290 ($[M-Na]^-$), found 502.1291.

(*Z*)-2-((*R*)-2-((*S*)-(4-(2-aminoethyl)-1H-imidazol-1-yl)(3,4-dihydroxyphenyl) methyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (–)-28b



Following the same procedure as that for the synthesis of **22**, starting from compound (–)-**27b** (20.0 mg, 0.0195 mmol), the corresponding compound (–)-**28b** (7.80 mg, 72% for two steps) was obtained as a yellow gum; $[\alpha]^{20}_{D}$ –7.5 (*c* 0.45, CH_3OH); ^1H NMR (CD_3OD, 500 MHz) δ 8.37 (s, 1H), 7.30 (s, 1H), 7.07 (s, 1H), 7.03 (d, *J* = 1.7 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.94 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.89 (d, *J* = 2.7 Hz, 1H), 6.83 (dd, *J* = 8.1, 4.1 Hz, 2H), 6.68 (d, *J* = 6.5 Hz, 1H), 5.96 (d, *J* = 6.5 Hz, 1H), 5.82 (d, *J* = 2.4 Hz, 1H), 3.07 (t, *J* = 7.4 Hz, 2H), 2.87 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 149.3, 149.2, 148.7, 147.9, 139.1, 135.4, 128.5, 126.2, 125.8, 125.2, 123.0, 122.5, 120.7, 118.2, 117.9 ,117.5, 111.6, 110.7, 110.3, 69.6 (q, 1C, *J* = 151.5 Hz, CH_2CF_3), 65.8, 40.4, 25.9; IR (neat, cm^{-1}) υ_{max} 3127, 1690, 1502, 1423, 1275, 1040; HRMS (FAB) calcd for $C_{23}H_{23}F_3N_3O_8S$ 558.1163 ($[M+H]^+$), found 558.1168.

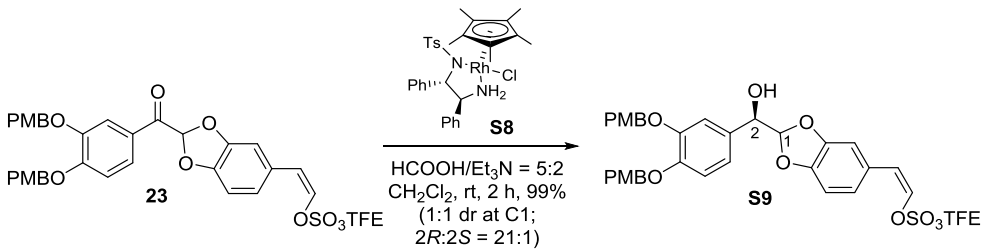
(–)-**Isowondonin B (4)**



Following the same procedure as that for the synthesis of (±)-wondonin A (**1**) and (±)-wondonin B (**2**), starting from compound (–)-**28b** (7.80 mg, 0.0139 mmol), the corresponding compound (–)-isowondonin B (**4**) (4.40 mg, 60% for two steps) was obtained as a yellow gum; $[\alpha]^{20}_{D}$ –4.5 (*c* 0.65, CH_3OH); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.51 (s, 1H), 7.15 (d, *J* = 1.2 Hz, 1H), 7.03 (s, 2H), 6.93 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.87 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 2.1 Hz, 1H), 6.65 (t, *J* = 7.6 Hz, 1H), 5.61 (s, 1H), 5.43 (d, *J* = 7.1 Hz, 1H), 2.96 (t, *J* = 7.4 Hz, 2H), 2.80–2.74 (m, 2H), 2.71 (s, 6H); ^{13}C NMR (CD_3OD, 150 MHz) δ 149.1, 148.2, 148.1, 147.7, 140.1, 138.8, 137.6, 131.1, 127.0, 124.4, 122.3, 120.5, 117.8, 117.4, 111.6, 111.5, 110.4, 109.4, 65.4, 59.5, 44.4, 24.6; IR (neat, cm^{-1}) υ_{max} 3460 (br), 2927, 1610, 1502, 1275, 1110, 1034; HRMS (Q-TOF) calcd for $C_{23}H_{24}N_3O_8S$ 502.1290 ($[M\text{-}Na]^-$), found 502.1302.

IV-4. Synthesis of (+)-28a and (+)-28b

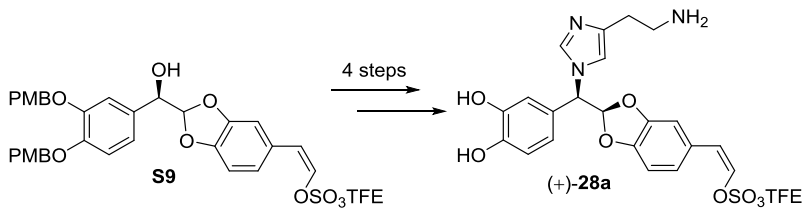
(*Z*)-2-(2-((*R*)-(3,4-bis((4-methoxybenzyl)oxy)phenyl)(hydroxy)methyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (S9)



Following the same procedure as that for the synthesis of **25**, starting from compound **23** (600 mg, 0.853 mmol), using Noyori's (*S*,*S*)-RhTsDPEN catalyst **S8**, the corresponding compound **S9** (594 mg, 99%, 1:1 dr at C1) as a yellow oil; The absolute configuration at C2 was assigned as *R* with a *R*/*S* ratio of 21/1 by Mosher analysis; ^{1}H NMR ($CDCl_3$, 500 MHz; two diastereomers in a 1:1 ratio) δ 7.33 (t, *J* = 8.6 Hz, 4H), 7.07–6.85 (m, 10H), 6.75 (dd, *J* = 16.8, 13.1 Hz, 1H), 6.57 (dd, *J* = 6.5, 2.5 Hz, 1H), 6.12 (d, *J* = 4.5 Hz, 1H), 5.84 (dd, *J* = 6.5, 2.3 Hz, 1H), 5.07 (s, 2H), 5.05 (s, 2H), 4.80 (br s, 1H), 4.50–4.44 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz; diastereomer 1/diastereomer 2) δ 159.3, 149.5, 149.1/149.0, 148.0/147.9, 147.8/147.7, 132.9, 129.9, 129.2/129.1, 128.9, 125.5, 124.0, 122.3, 121.8, 120.4/120.3, 120.1, 116.7, 115.0, 114.3/114.2, 113.9, 112.1, 109.0/108.9, 108.4/108.3, 73.9, 71.3/71.2, 67.3 (q, 1C, *J* = 154.0 Hz, CH_2CF_3),

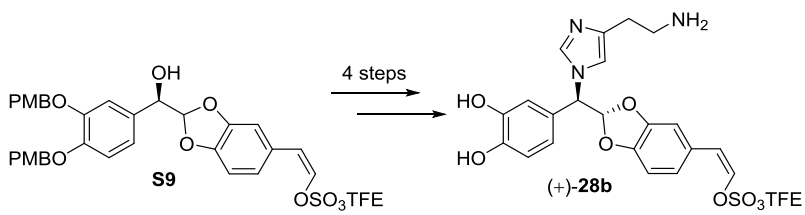
55.2;, IR (neat, cm^{-1}) υ_{max} 3500, 1602, 1513, 1425, 1210, 1174, 1034, 817; HRMS (FAB) calcd for $C_{34}H_{31}F_3O_{11}S$ 704.1539 (M^+), found 704.1532.

(*Z*)-2-((*R*)-2-((*R*)-(4-(2-aminoethyl)-1H-imidazol-1-yl)(3,4-dihydroxyphenyl) methyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (+)-28a.



Following the same procedure as that for the synthesis of (−)-**28a**, starting from compound **S9** (210 mg, 0.298 mmol), the corresponding compound (+)-**28a** (8.4 mg, 5% for four steps) was obtained as a yellow gum; $[\alpha]^{20}_D$ +9.7 (*c* 0.45, CH_3OH); ^1H NMR (CD_3OD, 400 MHz) δ 8.42 (s, 1H), 7.34 (s, 1H), 7.12 (d, *J* = 1.4 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.98–6.88 (m, 3H), 6.83–6.78 (m, 3H), 6.88 (d, *J* = 3.1 Hz, 1H), 6.69 (d, *J* = 6.6 Hz, 2H), 5.97 (d, *J* = 6.6 Hz, 1H), 5.84 (d, *J* = 2.7 Hz, 1H), 4.93–4.88 (m, 2H), 3.11–3.06 (m, 2H), 2.92–2.90 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 149.4, 149.1, 148.6, 147.8, 139.1, 135.4, 128.4, 126.4, 125.9, 125.5, 122.5, 122.4, 120.6, 118.2, 117.8 ,117.5, 111.6, 110.8, 110.2, 69.6 (q, 1C, *J* = 151.5 Hz, CH_2CF_3), 66.7, 40.7, 25.9; IR (neat, cm^{-1}) υ_{max} 3125, 1682, 1507, 1423, 1255, 1044; HRMS (FAB) calcd for $C_{23}H_{23}F_3N_3O_8S$ 558.1163 ($[M+H]^+$), found 558.1161.

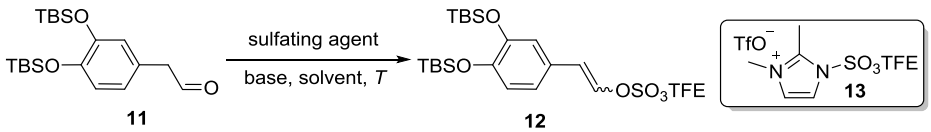
(*Z*)-2-((*S*)-2-((*R*)-(4-(2-aminoethyl)-1H-imidazol-1-yl)(3,4-dihydroxyphenyl) methyl)benzo[*d*][1,3]dioxol-5-yl)vinyl (2,2,2-trifluoroethyl) sulfate (+)-28b



Following the same procedure as that for the synthesis of (−)-**28b**, starting from compound **S9** (210 mg, 0.298 mmol), the corresponding compound (+)-**28b** (7.1 mg, 4.3% for four steps) was obtained as a yellow gum; $[\alpha]^{20}_{D}$ +8.3 (*c* 0.45, CH_3OH); ^1H NMR (CD_3OD, 800 MHz) δ 8.47 (s, 1H), 7.34 (s, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 7.04 (d, *J* = 2.1 Hz, 1H), 6.97 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.95 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.89 (d, *J* = 2.8 Hz, 1H), 6.83 (dd, *J* = 8.2, 6.1 Hz, 2H), 6.68 (d, *J* = 6.6 Hz, 1H), 5.96 (d, *J* = 6.6 Hz, 1H), 5.85 (d, *J* = 2.8 Hz, 1H), 4.90–4.88 (m, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.89 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (CD_3OD, 200 MHz) δ 149.3, 149.1, 148.7, 147.9, 138.9, 135.5, 134.5, 128.6, 126.2, 125.5, 124.8, 123.4, 122.5, 121.0, 118.2, 117.9 ,117.5, 111.4, 110.8, 110.3, 69.6 (q, 1C, *J* = 151.6 Hz, CH_2CF_3), 66.0, 40.4, 25.6; IR (neat, cm^{-1}) υ_{max} 3127, 1690, 1502, 1423, 1275, 1040; HRMS (FAB) calcd for $C_{23}H_{23}F_3N_3O_8S$ 558.1163 ($[M+H]^+$), found 558.1158.

IV-5. Study of the selective formation of styryl sulfate

Table S1. Additional conditions tested to optimize the selective formation of **12**



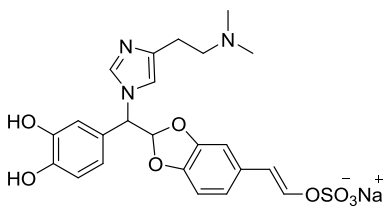
entry	sulfating agent (eq)	base (eq)	solvent	*T* (ºC)	yield (%),[a] *Z*:*E*
1	$ClSO_3TFE$ (4)	TEA (4)	THF	rt	0
2	$ClSO_3TFE$ (4)	DIPEA (4)	THF	rt	0
3	$ClSO_3TFE$ (4)	DIPEA (4)	THF	rt to 50	0
4	$ClSO_3TFE$ (4)	DBU (4)	THF	rt	0
5	$ClSO_3TFE$ (4)	DBU (4)	THF	rt to 50	0
6	**13** (2)	2,6-Lutidine (2)	THF	rt	0
7	**13** (2)	2,6-Lutidine (2)	CH_3CN	rt to 70	0
8	**13** (2)	DIPEA (2)	CH_3CN	rt	0
9	**13** (2)	DIPEA (2)	CH_3CN	rt o 70	52%, 2:1
10	**13** (4)	TEA (4)	THF	rt	31%, 1:1
11	**13** (4)	DIPEA (4)	THF	rt	36%, 1:1
12	**13** (4)	DBU (2)	THF	rt	93%, 1:1
13	**13** (4)	DBU (2)	THF	0	90%, 2:1
14	**13** (4)	DBU (2)	THF	–78	88%, 5:1
15	**13** (4)	DBU (2)	THF	–90	92%, 6:1
16	**13** (4)	*t*-BuOK (2)	THF	rt	15%, 1:2
17	**13** (4)	*t*-BuOK (2)	THF	–78	50%, 1:4
18	**13** (4)	*t*-BuOK (2)	THF	–95	63%, 1:8.5

[a]Isolated yield.

IV-6. Data comparison between natural and synthetic (±)-wondonin A (1), (±)-wondonin B (2), (−)-isowondonin A (3) and (−)-isowondonin B (4)

The spectra of our synthetic (±)-wondonin A (**1**), (±)-wondonin B (**2**), (−)-isowondonin A (**3**) and (−)-isowondonin B (**4**) compound were compared with reported spectra of natural wondonins and isowondonins.[1]

I. Data comparison between natural and synthetic (±)-wondonin A (1)

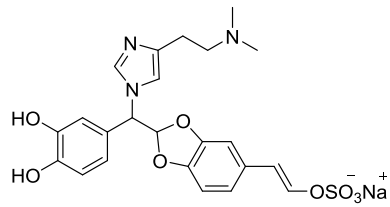


(±)-wondonin A (**1**)

^{1}H NMR		**^{13}C NMR**	
Natural (300 MHz, CD_3OD)	**Synthetic (500 MHz, CD_3OD)**	**Natural (75 MHz, CD_3OD)**	**Synthetic (150 MHz, CD_3OD)**
7.61 (s, 1H)	7.61 (s, 1H)	149.0	149.8
7.14 (d, *J* = 12.5 Hz, 1H)	7.14 (d, *J* = 12.5 Hz, 1H)	147.5	148.3
7.00 (d, *J* = 2.2 Hz, 1H)	7.01 (d, *J* = 1.8 Hz, 1H)	147.3	148.1
6.92 (s, 1H)	6.92 (s, 1H)	146.9	147.7
6.90 (dd, *J* = 8.3, 2.2 Hz, 1H)	6.91 (m, 1H)	140.0	140.8
6.81 (d, *J* = 2.0 Hz, 1H)	6.82 (s, 1H)	139.4	140.2
6.81 (d, *J* = 8.3 Hz, 1H)	6.81 (d, *J* = 8.6 Hz, 1H)	138.1	138.7

6.79 (d, *J* = 1.5 Hz, 1H)	6.79 (d, *J* = 0.7 Hz, 1H)	130.3	131.1
6.65 (dd, *J* = 8.1, 1.5 Hz, 1H)	6.64 (dd, *J* = 8.0, 0.7 Hz, 1H)	126.5	127.3
6.60 (d, *J* = 8.1 Hz, 1H)	6.59 (d, *J* = 8.0 Hz, 1H)	121.5	122.2
6.11 (d, *J* = 12.5 Hz, 1H)	6.11 (d, *J* = 12.5 Hz, 1H)	121.3	122.1
5.58 (d, *J* = 2.0 Hz, 1H)	5.58 (s, 1H)	118.4	119.3
2.82 (t, *J* = 7.1 Hz, 2H)	2.92 (t, *J* = 7.6 Hz, 2H)	116.9	117.7
2.68–2.72 (m, 2H)	2.76 (m, 2H)	116.6	117.4
2.62 (s, 6H)	2.72 (s, 6H)	115.4	116.2
		110.9	111.7
		109.6	109.8
		105.9	106.7
		64.3	65.2
		59.3	60.0
		44.2	44.8
		24.9	25.3

II. Data comparison between natural and synthetic (±)-wondonin B (2)

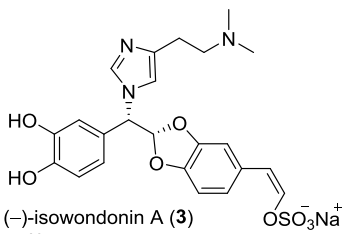


(±)-wondonin B (**2**)

^{1}H NMR		^{13}C NMR	
Natural (300 MHz, CD_3OD)	**Synthetic (500 MHz, CD_3OD)**	**Natural (75 MHz, CD_3OD)**	**Synthetic (125 MHz, CD_3OD)**
7.56 (d, *J* = 1.0 Hz, 1H)	7.56 (s, 1H)	148.9	149.7
7.13 (d, *J* = 12.7 Hz, 1H)	7.13 (d, *J* = 12.5 Hz, 1H)	147.6	148.4
6.99 (d, *J* = 2.2 Hz, 1H)	7.00 (s, 1H)	147.3	148.1
6.98 (br s, 1H)	7.00 (s, 1H)	146.8	147.6
6.89 (dd, *J* = 8.3, 2.2 Hz, 1H)	6.90 (dd, *J* = 8.2, 1.3 Hz, 1H)	140.0	140.9
6.80 (d, *J* = 8.3 Hz, 1H)	6.80 (d, *J* = 8.2 Hz, 1H)	139.0	139.9
6.79 (d, *J* = 2.4 Hz, 1H)	6.79 (s, 1H)	138.2	138.5
6.74 (br s, 1H)	6.73 (s, 1H)	130.6	131.3
6.66 (d, *J* = 2.0 Hz, 1H)	6.66 (br s, 1H)	126.4	127.2
6.66 (s, 1H)	6.66 (br s, 1H)	121.4	122.2
6.09 (d, *J* = 12.7 Hz, 1H)	6.09 (d, *J* = 12.5 Hz, 1H)	121.0	121.8
5.58 (d, *J* = 2.4 Hz, 1H)	5.59 (s, 1H)	118.7	119.7
2.76 (m, 2H)	2.90 (t, *J* = 7.4 Hz, 2H)	116.9	117.7
2.68–2.71 (m, 2H)	2.72 (m, 2H)	116.5	117.4
2.55 (s, 6H)	2.66 (s, 6H)	115.3	116.1
		110.9	111.7

	109.2	109.9
	105.9	106.7
	64.3	65.1
	59.4	60.0
	44.3	44.8
	25.0	25.5

III. Data comparison between natural and synthetic (−)-isowondonin A (3)

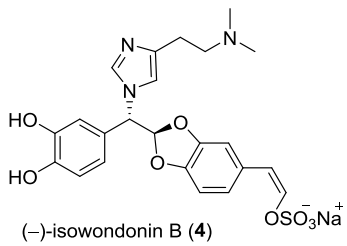


(−)-isowondonin A (**3**)
$[\alpha]^{20}_{D}$ –4.2 (*c* 0.72, CH_3OH)
lit. $[\alpha]^{20}_{D}$ –4.0 (*c* 0.72, CH_3OH)

^{1}H NMR		**^{13}C NMR**	
Natural (300 MHz, CD_3OD)	**Synthetic (600 MHz, CD_3OD)**	**Natural (75MHz, CD_3OD)**	**Synthetic (150 MHz, CD_3OD)**
7.60 (s, 1H)	7.62 (s, 1H)	148.5	149.3
7.31 (d, *J* = 1.3 Hz, 1H)	7.31 (d, *J* = 1.2 Hz, 1H)	147.5	148.2
7.04 (d, *J* = 1.9 Hz, 1H)	7.07 (d, *J* = 1.6 Hz, 1H)	147.1	147.8
6.92 (s, 1H)	6.95–6.94 (m, 1H)	146.9	147.7
6.91 (dd, 1H)	6.95–6.94 (m, 1H)	139.2	140.5
6.81 (d, *J* = 8.1 Hz, 1H)	6.83–6.81 (m, 1H)	137.9	138.7
6.80 (br d, *J* = 8.1 Hz, 1H)	6.83–6.81 (m, 1H)	134.5	137.8
6.79 (d, *J* = 1.7 Hz, 1H)	6.75 (dd, *J* = 8.1, 1.0 Hz, 1H)	130.3	130.8

6.64 (d, *J* = 7.1 Hz, 1H)	6.64 (d, J = 7.0 Hz, 1H)	126.6	127.2
6.60 (d, *J* = 8.1 Hz, 1H)	6.59 (d, *J* = 8.1 Hz, 1H)	123.8	124.6
5.57 (d, *J* = 1.7 Hz, 1H)	5.58 (s, 1H)	121.6	122.4
5.44 (d, *J* = 7.1 Hz, 1H)	5.46 (d, *J* = 7.0 Hz, 1H)	118.3	119.6
2.70 (t, *J* = 7.1 Hz, 2H)	2.92–2.91 (m, 2H)	116.9	117.7
2.64–2.70 (m, 2H)	2.78–2.73 (m, 2H)	116.6	117.4
2.50 (s, 6H)	2.71 (s, 6H)	110.9	111.8
		110.8	111.6
		109.8	110.5
		108.5	109.3
		64.4	65.3
		59.4	59.4
		44.4	44.4
		25.3	24.8

IV. Data comparison between natural and synthetic (–)-isowondonin B (4)



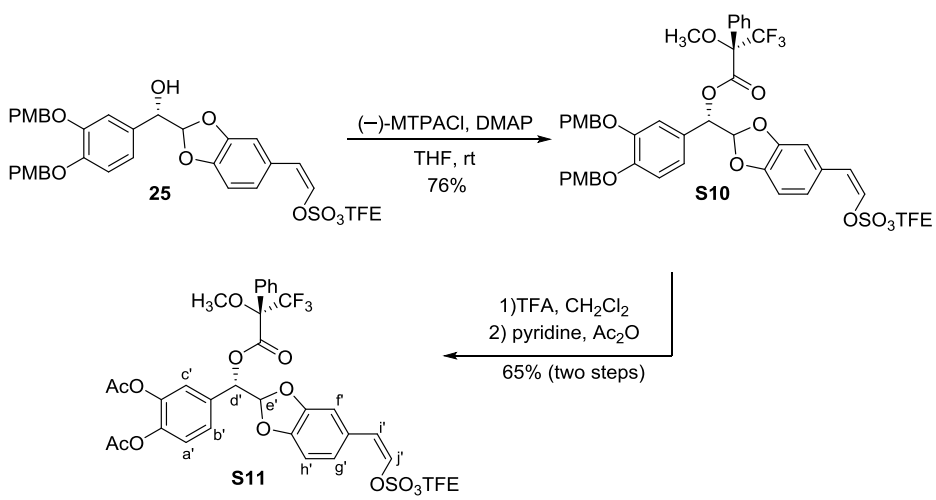
(–)-isowondonin B (**4**)
$[\alpha]^{20}_{D}$ –3.7 (*c* 0.65, CH_3OH)
lit. $[\alpha]^{20}_{D}$ –4.5 (*c* 0.65, CH_3OH)

^{1}H NMR		**^{13}C NMR**	
Natural (300 MHz, CD_3OD)	**Synthetic (500 MHz, CD_3OD)**	**Natural (75 MHz, CD_3OD)**	**Synthetic (150 MHz, CD_3OD)**
7.53 (s, 1H)	7.51 (s, 1H)	148.3	149.1
7.17 (d, *J* = 1.1 Hz, 1H)	7.15 (d, *J* = 1.2 Hz, 1H)	147.3	148.2
7.03 (br s, 1H)	7.03 (s, 1H)	147.2	148.1
7.03 (s, 1H)	7.03 (s, 1H)	146.8	147.7
6.93 (dd, 1H)	6.93 (dd, J = 8.2, 1.0 Hz, 1H)	139.0	140.1
6.88 (br d, *J* = 8.2 Hz, 1H)	6.87 (dd, J = 8.2, 1.2 Hz, 1H)	137.9	138.8
6.82 (d, *J* = 8.0 Hz, 1H)	6.82 (d, *J* = 8.0 Hz, 1H)	137.5	137.6
6.82 (d, *J* = 2.1 Hz, 1H)	6.82 (d, *J* = 2.1 Hz, 1H)	130.3	131.1
6.64 (d, *J* = 7.1 Hz, 1H)	6.65 (t, *J* = 7.6 Hz, 1H)	126.3	127.0
6.60 (d, *J* = 8.1Hz, 1H)	6.65 (t, *J* = 7.6 Hz, 1H)	123.6	124.4
5.61 (d, *J* = 2.1 Hz, 1H)	5.61 (s, 1H)	121.5	122.3
5.44 (d, *J* = 7.1 Hz, 1H)	5.43 (d, *J* = 7.1 Hz, 1H)	119.3	120.5
2.88 (m, 2H)	2.96 (t, J = 7.4 Hz, 2H)	116.9	117.8
2.76–2.71 (m, 2H)	2.80–2.74 (m, 2H)	116.5	117.4
2.64 (s, 6H)	2.71 (s, 6H)	110.8	111.6

	110.6	111.5
	109.6	110.4
	108.6	109.4
	64.4	65.4
	59.4	59.5
	44.4	44.4
	25.3	24.6

IV-7. Absolute configuration determination of the stereogenic center at C2

4-((1*S*)-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)(5-((*Z*)-2-(((2,2,2-trifluoroethoxy)sulfonyl)oxy)vinyl)benzo[*d*][1,3]dioxol-2-yl)methyl)-1,2-phenylene diacetate (S11)



A solution of **25** (30.0 mg, 0.0426 mmol), 4-dimethylaminopyridine (5.20 mg,

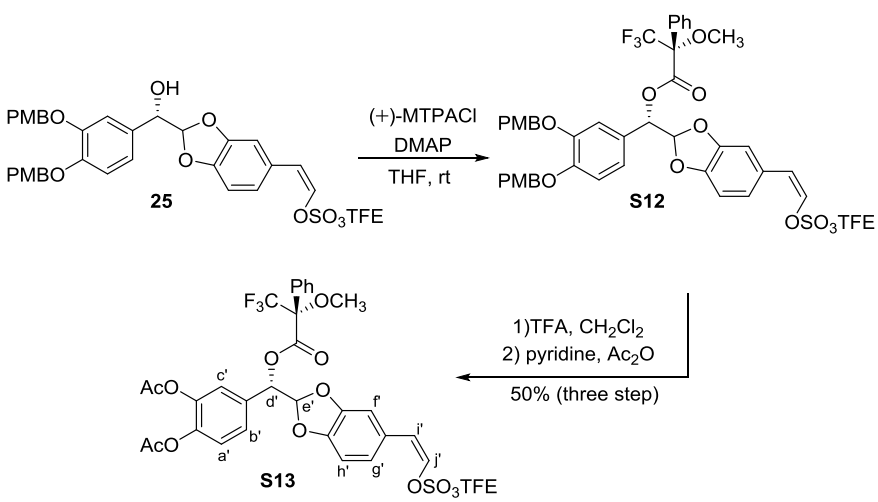
0.0511 mmol), (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.00950mL, 0.0511 mmol) in THF (0.4 mL) was stirred at rt for 4 h. The reaction mixture was purified by silica gel column chromatography (hexane/EtOAc, 3:1) to yield **S10** (29.0 mg, 76%) as a yellow oil; ^{1}H NMR (CD_3Cl, 400 MHz) δ 7.34–7.28 (m, 9H), 7.02–6.72 (m, 11H), 6.28 (d, *J* = 4.0 Hz, 1H), 6.04 (d, *J* = 4.0 Hz, 1H), 5.84 (d, *J* = 6.3 Hz, 1H), 5.05 (s, 2H), 4.93–4.88 (m, 2H), 4.49–4.43 (m, 2H), 3.45(s, 3H);

To a solution of the above compound **S10** (21.0 mg, 0.0228 mmol) in CH_2Cl_2 (0.4 mL) at rt, TFA (0.1 mL) was added. The reaction mixture was stirred at rt for 10 min. Then, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the corresponding catechol (15.0 mg) as a yellow oil;

To a solution of the above catechol (15.0 mg) in Ac_2O (0.3 mL), pyridine (0.012 mL) was added. The mixture was stirred at rt for 30 min. Then, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 3:1) to yield **S11** (12.0 mg, 65% for two steps) as a yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36–7.28 (m, 5H), 7.20 (dd,

J = 8.2, 2.2 Hz, 0.5H), 7.19 (dd, *J* = 8.2, 2.2 Hz, 0.5H), 7.16 (d, *J* = 8.2 Hz, 0.5H), 7.15 (d, *J* = 8.2 Hz, 0.5H), 7.11 (d, *J* = 2.8 Hz, 1H), 7.03 (d, *J* = 1.3 Hz, 0.5H), 7.01 (d, *J* = 1.8 Hz, 0.5H), 6.92 (dd, *J* = 8.2, 1.8 Hz, 0.5H), 6.90 (dd, *J* = 8.2, 1.8 Hz, 0.5H), 6.76 (d, *J* = 8.2 Hz, 0.5H), 6.74 (d, *J* = 8.2 Hz, 0.5H), 6.58 (d, *J* = 6.9 Hz, 0.5H), 6.33–6.31 (m, 1H), 6.14–6.12 (m, 1H), 5.84 (d, *J* = 6.9 Hz, 0.5H), 5.81 (d, *J* = 6.9 Hz, 0.5H), 4.49–4.45 (m, 2H), 3.46 (s, 3H), 2.28–2.24 (m, 6H).

4-((1*S*)-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)(5-((*Z*)-2-(((2,2,2-trifluoroethoxy)sulfonyl)oxy)vinyl)benzo[*d*][1,3]dioxol-2-yl)methyl)-1,2-phenylene diacetate (S13)



Following the same procedure as that for the synthesis of (*S*)-Mosher ester **S11**, starting from compound **25** (30.0 mg, 0.0426 mmol) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.00950mL, 0.0511 mmol), the

corresponding (*R*)-Mosher ester **S13** (12.0 mg, 50% for three steps) was obtained as a yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37–7.28 (m, 7H), 7.22 (d, *J* = 8.2 Hz, 0.5H), 7.21 (d, *J* = 8.2 Hz, 0.5H), 7.00 (d, *J* = 1.3 Hz, 0.5H), 6.89 (dd, *J* = 8.2, 1.3 Hz, 0.5H), 6.86 (dd, *J* = 8.2, 1.3 Hz, 0.5H), 6.71 (d, *J* = 7.8 Hz, 0.5H), 6.57 (d, *J* = 6.9 Hz, 1H), 6.29–6.27 (m, 1H), 6.23–6.21 (m, 1H), 5.83 (d, *J* = 6.4 Hz, 0.5H), 5.81 (d, *J* = 6.4 Hz, 0.5H), 4.50–4.45 (m, 2H), 3.39 (s, 3H), 2.28–2.27 (m, 6H).

As shown in Figure S1, $H^{e'}$ in (*S*)-Mosher ester (**S11**) is in low field {compared to $H^{e'}$ in (*R*)-Mosher ester (**S13**)}, and $H^{b'}$ and $H^{c'}$ are high field. Therefore, the $\Delta\delta_{SR}$ of $H^{e'}$ is positive value, and $\Delta\delta_{SR}$ of $H^{b'}$ and $H^{c'}$ are negative values. Due to these values, the configuration of C2 was assigned as *S*. The comparisons of other protons are shown in Table S2 and are consistent with our analysis. Following the same procedure as that for the determination of C2 configuration of compound **25**, the C2 configuration of compound **S9** was assigned as *R*.

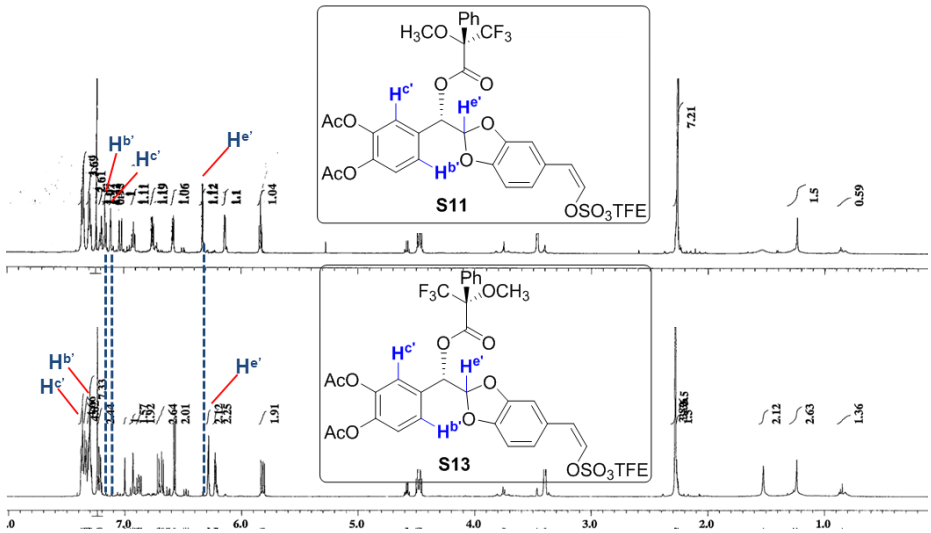


Figure S1. Comparison of the ^{1}H NMR spectra of **S11** and **S13**.

Table S2. Assignment of the absolute configuration of **25** by Mosher analysis of **S11** and **S13**.

Assignment	δ(*S*)-Mosher ester [ppm]	δ(*R*)-Mosher ester [ppm]	Δδ*SR*[ppm]
a'	7.16	7.34	-0.18
b'	7.19	7.22	-0.03
c'	7.11	7.32	-0.21
d'	6.13	6.22	-0.09
e'	6.32	6.28	+0.04
f'	7.03	6.96	+0.07
g'	6.92	6.87	+0.05
h'	6.75	6.69	+0.06
i'	6.58	6.57	+0.01
j'	5.83	5.81	+0.02

As shown in Figure S2, the proton of –OMe {from (–)-MTPA} in the ^{1}H NMR spectrum of the racemic Mosher ester is shown as two peaks with a 1:1 ratio. In comparison to this reference, the proton of –OMe {from (–)-MTPA} in the ^{1}H NMR spectrum of the (*S*)-Mosher ester (**S10**) is displayed as two peaks with a 19:1 ratio. Therefore, the 2*S*/2*R* ratio of compound **25** is 19:1. Following the same procedure as that for the determination of the 2*S*/2*R* ratio of compound **25**, the 2*S*/2*R* ratio of compound **S9** was displayed as 1:21.

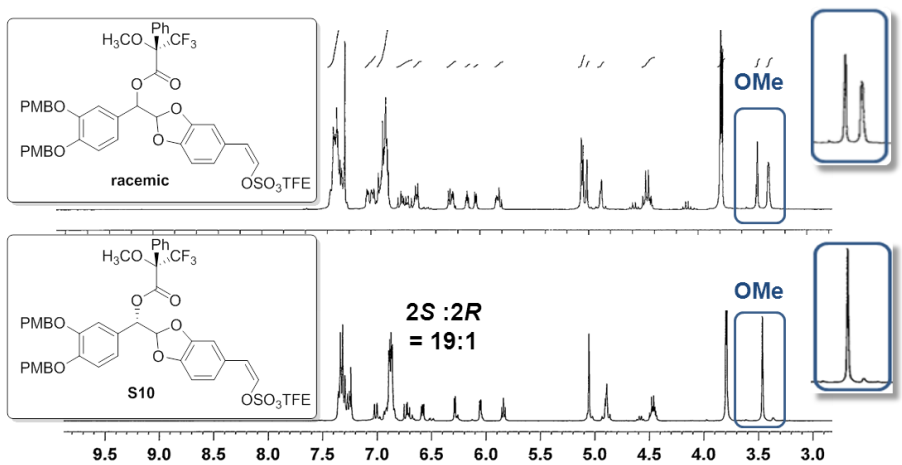


Figure. S2 Determination of the (2*S*/2*R*) ratio of compounds **25**.

IV-8. Chiral HPLC chromatograms of (–)-27a and (–)-27b

HPLC conditions: CHIRALCEL OD-H (0.46 × 25 cm), hexane/2-propanol = 60:40, flow rate = 0.4 mLmin^{-1}, λ = 254 nm. The retention times are shown in Figure S3.

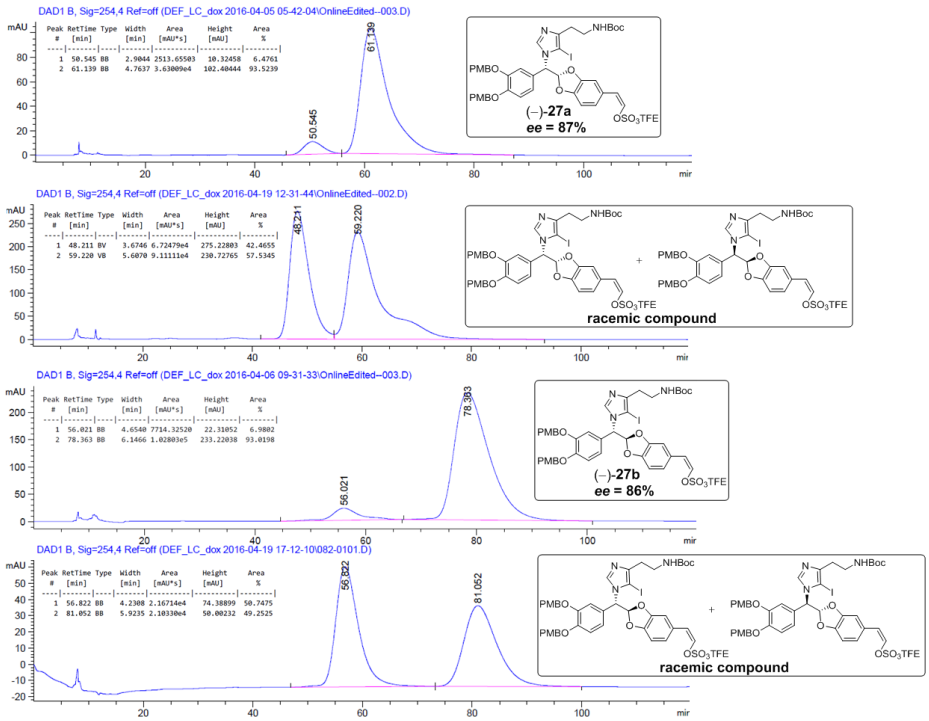


Figure S3. Chiral HPLC chromatograms of **(–)-27a and (–)-27b**.

IV-9. Calculation of the nucleophilicity of the amine

Theoretical background of Fukui fuction

Local softness is a widely used local density functional descriptor for comparing the reactivity of different sites within one molecule. Local softness is given by

$$s(r) = Sf(r)$$

where S is the global softness and $f(r)$ is the Fukui function.[21] The global softness can be approximated as

$$S = 1 / (\mathrm{IP} - \mathrm{EA})$$

where IP and EA are the ionization potential and electron affinity respectively, of the chemical species.

The Fukui function describes the variation in the electronic density ($\rho(r)$) upon changing the number of electrons (N) in the system.[22]

$$f(r) = [\partial\rho(r) / \partial N]_{v(r)}$$

Therefore, the Fukui functions for nucleophilic and electrophilic attacks on an atom k in an N electron system was introduced by Yang and Mortier[23] as

$$f_k^+ = \rho_k(N + 1) - \rho_k(N) \text{ (nucleophilic attack)}$$

$$f_k^- = \rho_k(N) - \rho_k(N - 1) \text{ (electrophilic attack)}$$

where $\rho_k(N+1)$, $\rho_k(\mathrm{N})$ and $\rho_k(N - 1)$ are the electronic populations on atom k in the $N+1$, N and $N-1$ electron systems, respectively. These functions can be condensed

to the nuclei using an atomic charge-partitioning scheme, such as Mulliken[24] population analysis. Therefore, the local softness for atom k can be written as

$$s_k^+ = [\rho_k(N + 1) - \rho_k(N)]S$$

$$s_k^- = [\rho_k(N) - \rho_k(N - 1)]S$$

The local softness is used as a reactivity index but does not always provide the correct reactivity trends. Therefore, new parameters have been developed by S. Pal[13] to provide the "relative electrophilicity" and "relative nucleophilicity".

$$\text{Relative electrophilicity} = s_k^+ / s_k^-$$

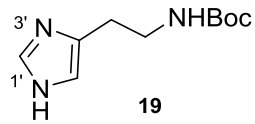
$$\text{Relative nucleophilicity} = s_k^- / s_k^+$$

This two relative values indicate to the preferable reactive sites in the reaction.

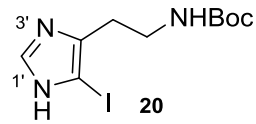
Geometry optimization and energy minimization of 19 and 20

The computational energy minimization of **19** and **20** was performed using the DMol3 program in Material Studio 2016. The Fukui function, ionization potential and electron affinity were also calculated using the DMol3 program.[25] In these calculations, we employed the generalized gradient approximation (GGA) in the Perdew-Burke-Ernzerhof (PBE)[26] form as well as a double numerical polarized (DNP) basis sets. To calculate the Fukui function values, a Mulliken partitioning scheme was employed. All of the molecules were modeled in the solvent phase (acetonitrile, COSMO).

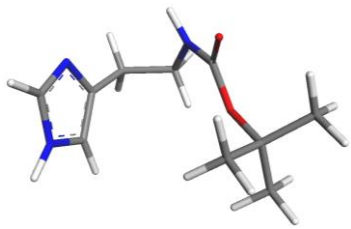
Table S3. Molecular energy of **19** and **20**

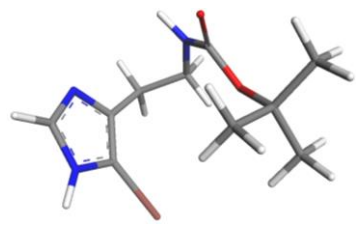


19



20





	Hartree (Ha)[a]	Ionization potential (eV)	Electron affinity (eV)	Global softness (eV^{-1})[b]
19	-705.4437493	7.38289488156	-1.28066843670	0.115425947
20	-7624.913896	7.37354232871	0.87656305006	0.153917683

[a] 1Ha = 627.509391 kcal/mol. [b] Global softness = 1 / (Ionization potential - Electron affinity)

Table S4. Molecular property of **19** and **20**.

	Atom	Fukui function (–)	Fukui function (+)	Local softness (S–)[a]	Local softness (S+)	Relative nucleophilicity[b]
19	N1'	0.014	0.047	0.0016	0.0054	0.3
	N3'	0.040	0.087	0.0046	0.010	0.5
20	N1'	0.014	0.004	0.0022	0.00062	3.5
	N3'	0.038	0.054	0.0058	0.0083	0.7

[a] Local softness = Global softness x Fukui function. [b] Relative nucleophilicity = Local softness (S-) / Local softness (S+)

Calculation input

All calculations are performed under following conditions.

Task parameters

Calculate	optimize
Opt energy convergence	1.0000e–005
Opt gradient convergence	2.0000e–003 A
Opt displacement convergence	5.0000e–003 A
Opt iterations	50
Opt max displacement	0.3000 A
Initial hessian	improved
Symmetry	off
Max memory	2048
File usage	smart
Scf density convergence	1.000000e-006
Scf charge mixing	2.000000e-001
Scf diis	6 pulay
Scf iterations	50

Electronic parameters

Spin polarization	restricted
Charge	0
Basis	dnp
Pseudopotential	none
Functional	pbe
Aux density	hexadecapole
Integration grid	fine
Occupation	fermi
Cutoff Global	4.4000 angstrom

Calculated properties

Plot	density
Plot	potential
Plot	fukuip
Plot	fukuim
Plot	fukui0
Mulliken analysis	charge
Esp fit	on
Bond orders	on
Grid	msbox 3 0.2500 0.2500 0.2500 3.0000

Calculation output

19

Atom	X	Y	Z	Atom	X	Y	Z
N	3.140162	8.222039	2.0833	H	1.621229	8.394204	4.778759
C	2.884664	7.846488	0.84281	O	-0.57552	7.616069	4.101617
N	3.155932	6.517348	0.659351	O	0.365655	5.524524	4.426956
C	3.615725	6.019477	1.863807	C	-0.82638	4.784933	3.950835
C	3.596365	7.090964	2.734883	C	-0.38008	3.327598	4.077694
C	3.935096	7.124021	4.192173	C	-1.11785	5.129292	2.489453
C	2.790277	6.645913	5.108651	C	-2.01993	5.064742	4.864687
N	1.553802	7.387312	4.900879	H	-0.12646	3.08877	5.119776
H	2.513841	8.481588	0.043671	H	0.503957	3.138569	3.45274
H	3.052693	5.994231	-0.20348	H	-1.1878	2.657671	3.75312
H	3.900088	4.980138	1.986286	H	-0.22229	4.955114	1.874943
H	4.203075	8.159928	4.451355	H	-1.42414	6.175652	2.3845
H	4.821866	6.505544	4.404483	H	-1.92348	4.480422	2.116449
H	3.110046	6.740081	6.161118	H	-2.3196	6.116747	4.807528
H	2.570434	5.588654	4.925931	H	-1.76591	4.819601	5.905769
C	0.360572	6.895179	4.431947	H	-2.86798	4.434056	4.561559

Total energy = -705.4437493 Ha

20

Atom	X	Y	Z	Atom	X	Y	Z
N	3.031892	8.382621	2.039794	H	1.585279	8.434005	4.841628
C	2.725054	8.056681	0.794684	O	-0.61197	7.642124	4.183634
N	2.965533	6.732615	0.555127	O	0.370889	5.55714	4.409029
C	3.460669	6.197797	1.730484	C	-0.80964	4.808394	3.915808
C	3.497905	7.231716	2.648015	C	-0.3323	3.356888	3.994169
C	3.89769	7.214934	4.087645	C	-1.11193	5.197684	2.465983
C	2.798778	6.693968	5.037377	C	-2.00374	5.036363	4.842613
N	1.544123	7.420201	4.909278	H	-0.06739	3.093208	5.028068
H	2.33219	8.728273	0.036471	H	0.55171	3.204776	3.358439
H	2.83133	6.222873	-0.31282	H	-1.12975	2.680899	3.655858
I	3.990069	4.16143	1.884084	H	-0.21369	5.061165	1.845211
H	4.171937	8.244611	4.365477	H	-1.43934	6.241539	2.400407
H	4.795683	6.592859	4.233959	H	-1.90601	4.547032	2.071047
H	3.168487	6.760222	6.07569	H	-2.32689	6.083135	4.815654
H	2.588795	5.638535	4.832329	H	-1.73758	4.770362	5.876099
C	0.342693	6.923945	4.463327	H	-2.8396	4.394969	4.527477

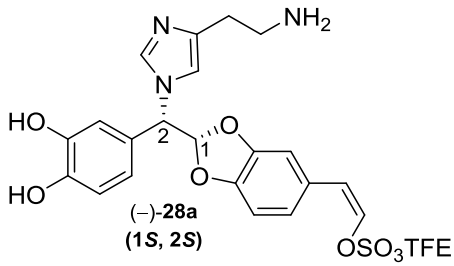
Total energy = -7624.913896 Ha

IV-10. Determine absolute configuration using ECD analysis

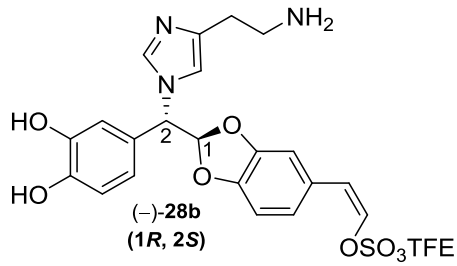
Geometry optimization and ECD calculation of 28a and 28b

The computational energy minimization of **28** was performed using the DMol3 program in Material Studio 2016. In these calculations, we employed generalized gradient approximation (GGA) in the Perdew-Burke-Ernzerhof (PBE) form as well as a double numerical plus d-functions (DND) basis sets. The ECD spectra were calculated with TD-DFT (time-dependent density functional theory) using the B3LYP functional and the DGTZVP basis sets as implemented in Gaussian 09.[27] The number of excited states per molecule was 30. The solvent effects were taken into account using the polarizable continuum model (PCM, CH_3OH). The ECD spectra were generated by the SpecDis[28] program using a Gaussian band shape with a 0.16 eV exponential half-width from the dipole-length dipolar and rotational strengths.

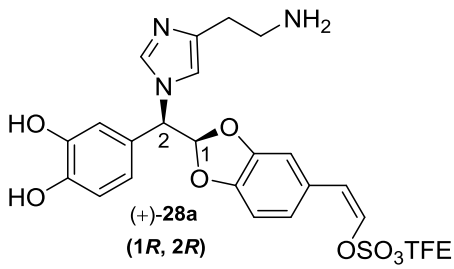
Table S5. Molecular energy of **28**.



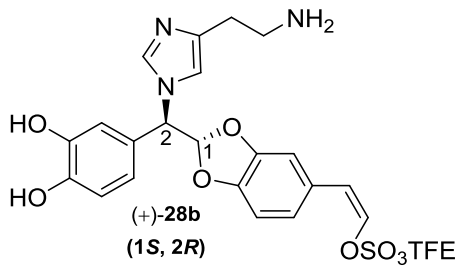
(–)-**28a**
(**1*S*, 2*S***)



(–)-**28b**
(**1*R*, 2*S***)



(+)-**28a**
(**1*R*, 2*R***)



(+)-**28b**
(**1*S*, 2*R***)

	(–)-28a	**(–)-28b**	**(+)-28a**	**(+)-28b**
Hartree (Ha)[a]	-2351.767013	-2351.768769	-2351.766731	-2351.768610

[a] 1Ha = 627.509391 kcal/mol.

Calculation input

All calculations are performed under following conditions.

Task parameters

Calculate	optimize
Opt energy convergence	2.0000e–005
Opt gradient convergence	4.0000e–003 A
Opt displacement convergence	5.0000e–003 A
Opt iterations	50
Opt max displacement	0.3000 A
Initial hessian	improved
Symmetry	off
Max memory	2048
File usage	smart
Scf density convergence	1.000000e-005

Scf charge mixing	2.000000e-001
Scf diis	6 pulay
Scf iterations	50

Electronic parameters

Spin polarization	restricted
Charge	0
Basis	dnd
Pseudopotential	none
Functional	pbe
Aux density	hexadecapole
Integration grid	medium
Occupation	thermal 0.0050
Cutoff Global	3.6000 angstrom

Calculated properties

Calculation output

(–)-28a

Atom	X	Y	Z	Atom	X	Y	Z
C	21.84466	-29.1181	1.383981	O	21.45367	-22.7953	-8.65405
C	22.93624	-28.6894	2.163341	O	21.50449	-23.6437	-6.24419
C	23.60514	-27.518	1.803733	O	21.77898	-25.197	-8.23914
C	23.2056	-26.7705	0.696995	H	24.45537	-27.1881	2.408433
C	22.11876	-27.1836	-0.08001	H	23.75258	-25.8621	0.433079
C	21.45386	-28.3671	0.275958	H	20.62447	-28.7459	-0.32668
O	21.22537	-30.2813	1.758096	H	20.50705	-30.4622	1.115281
O	23.28516	-29.4641	3.236874	H	24.06185	-29.0486	3.668446
C	21.70947	-26.3374	-1.27848	H	21.50926	-25.3114	-0.92272
C	20.39249	-26.7591	-1.94612	H	19.60072	-26.8486	-1.18021
N	22.79763	-26.206	-2.24719	H	20.21985	-29.7219	-4.86331
O	20.49874	-28.0206	-2.64526	H	19.3762	-28.8345	-7.04877
C	20.06468	-27.7779	-3.93092	H	19.04029	-24.8505	-5.35921
C	19.74388	-26.4308	-4.0792	H	18.21476	-27.0863	-8.31079
O	19.98274	-25.7611	-2.89952	H	23.41388	-28.2624	-2.49186
C	19.95222	-28.6714	-4.97892	H	22.75341	-24.0854	-2.63627
C	19.4762	-28.1603	-6.1957	H	25.32454	-27.0063	-5.62091
C	19.12974	-26.8039	-6.35707	H	25.38907	-28.3608	-4.48275
C	19.27415	-25.9092	-5.26396	H	27.01389	-27.0585	-3.06669
C	18.70792	-26.3405	-7.67967	H	26.88912	-25.6987	-4.20259
C	23.53436	-27.2346	-2.81766	H	18.56664	-24.9677	-9.3079
C	24.38098	-26.6388	-3.72628	C	22.38223	-26.1053	-7.28713
N	24.15721	-25.2709	-3.75109	C	22.81486	-27.3222	-8.08967
C	23.20477	-25.0482	-2.8678	H	21.66137	-26.4235	-6.52433
C	25.45808	-27.2615	-4.55663	H	23.25837	-25.6456	-6.80998
C	26.85821	-26.7975	-4.13594	F	23.74829	-27.0206	-9.02515
N	27.87276	-27.3364	-5.05047	F	23.35312	-28.2411	-7.24097
C	18.902	-25.1576	-8.2864	F	21.77085	-27.9141	-8.72963
O	19.50992	-24.0458	-7.70517	H	28.79442	-26.9557	-4.80233

S	21.16503	-23.7981	-7.64932	H	27.94942	-28.3538	-4.91966

Total energy = -2351.767013 Ha

(–)-28b

Atom	X	Y	Z	Atom	X	Y	Z
C	15.71327	-16.749	1.390654	O	24.60962	-20.4589	-7.32328
C	16.28645	-16.6872	2.67936	O	22.35502	-19.4933	-8.02204
C	17.67373	-16.6536	2.801331	O	22.72272	-22.0016	-7.96185
C	18.49375	-16.6764	1.672315	H	18.11887	-16.6163	3.800784
C	17.93946	-16.7254	0.392042	H	19.57888	-16.6529	1.79707
C	16.54133	-16.764	0.270361	H	16.0682	-16.8143	-0.71523
O	14.34567	-16.7902	1.320292	H	14.09199	-16.8388	0.374257
O	15.42803	-16.6724	3.744959	H	15.96603	-16.6242	4.563915
C	18.86017	-16.752	-0.81418	H	19.88652	-16.9266	-0.45703
C	18.55653	-17.9068	-1.78918	H	17.57724	-17.7918	-2.28126
N	18.90408	-15.4789	-1.54014	H	19.553	-21.7046	-0.43186
O	18.5725	-19.1604	-1.07346	H	21.48091	-22.6818	-1.70047
C	19.59748	-19.8989	-1.61708	H	21.71848	-19.1252	-4.1785
C	20.19898	-19.1933	-2.65484	H	23.39565	-22.3925	-3.15566
O	19.56903	-17.9753	-2.81614	H	16.91048	-15.3247	-2.3795
C	20.03022	-21.1569	-1.24524	H	20.92783	-14.8728	-1.12766
C	21.11192	-21.6876	-1.96438	H	17.19682	-13.0657	-4.39385
C	21.73376	-20.9882	-3.01423	H	18.49498	-11.9413	-3.9459
C	21.26046	-19.6986	-3.37468	H	17.27535	-11.3263	-1.86452
C	22.83087	-21.6483	-3.72556	H	15.98389	-12.4779	-2.26433
C	17.88986	-14.8718	-2.26381	H	24.01113	-22.1373	-5.45339
C	18.41026	-13.6836	-2.73463	C	23.21768	-22.2448	-9.29133
N	19.71978	-13.5493	-2.31405	C	22.90388	-23.6921	-9.63349
C	19.98173	-14.6327	-1.60916	H	24.30754	-22.1031	-9.33857
C	17.72969	-12.6166	-3.5347	H	22.71313	-21.5928	-10.0193
C	16.7363	-11.789	-2.70801	F	23.5106	-24.5595	-8.78494
N	16.16683	-10.7103	-3.52503	F	21.57401	-23.9493	-9.60942
C	23.19198	-21.5715	-5.01288	F	23.35924	-23.9483	-10.8923
O	22.50792	-20.72	-5.90615	H	15.52497	-10.1465	-2.95396
S	23.15576	-20.515	-7.38068	H	15.59162	-11.1161	-4.27524

Total energy = -2351.768769 Ha

(+)-28a

Atom	X	Y	Z	Atom	X	Y	Z
C	-11.2779	-2.11649	1.259125	O	10.2786	0.289317	-4.45673
C	-12.7468	-0.34223	-0.07275	O	5.499103	-0.37908	-4.28571
C	-11.6409	1.000421	-2.05621	O	8.070453	0.799543	-0.40024
C	-9.12757	0.601311	-2.73708	H	-12.7831	2.383701	-3.08498
C	-7.65547	-1.16521	-1.43506	H	-8.30516	1.69036	-4.28665
C	-8.76285	-2.49916	0.571642	H	-7.65849	-3.84332	1.685069
O	-12.4198	-3.37165	3.214046	H	-11.1645	-4.49906	3.981086
O	-15.2013	-0.02589	0.681435	H	-15.965	1.27462	-0.39628
C	-4.9199	-1.55468	-2.24122	H	-4.9046	-2.05848	-4.26606
C	-3.57725	-3.78493	-0.95922	H	-4.74888	-5.50477	-1.13837
N	-3.45385	0.781402	-2.05716	H	-0.03874	-3.11937	6.032195
O	-3.08895	-3.34179	1.693006	H	4.604129	-3.99998	5.754027

C	-0.53612	-3.73958	2.025408	H	3.983165	-5.23341	-2.33117
C	0.59413	-4.31047	-0.28157	H	8.195554	-5.7837	3.443459
O	-1.18996	-4.2568	-2.17621	H	-4.38114	2.040526	1.714549
C	0.84792	-3.59709	4.235065	H	-1.53729	0.790661	-5.65349
C	3.444593	-4.09938	4.05025	H	1.31506	6.586451	0.991728
C	4.61131	-4.7143	1.736658	H	-1.49969	6.361574	2.786023
C	3.138079	-4.81181	-0.50399	H	-3.76093	8.909681	-0.5363
C	7.352168	-5.08072	1.690927	H	-0.92899	9.021741	-2.33457
C	-3.25165	2.353654	0.032503	H	11.07077	-4.8411	0.14721
C	-1.55373	4.213144	-0.62626	C	5.678438	1.630456	0.634003
N	-0.66008	3.782665	-3.05096	C	6.277103	2.714214	3.227085
C	-1.813	1.721163	-3.8403	H	4.360165	0.047621	0.860581
C	-0.76099	6.496312	0.839605	H	4.829006	3.100852	-0.55993
C	-1.66617	8.960325	-0.38928	F	7.82819	4.748693	3.103497
N	-0.65706	11.15279	0.980012	F	4.081997	3.457443	4.345803
C	9.047064	-4.54271	-0.12113	F	7.390719	0.985681	4.76948
O	8.46654	-3.6158	-2.51806	H	-1.15878	12.78267	0.05159
S	8.00847	-0.55596	-3.18154	H	-1.49421	11.26938	2.730465

Total energy = -2351.766731 Ha

(+)-28b

Atom	X	Y	Z	Atom	X	Y	Z
C	-11.8781	-3.48088	2.555288	O	11.15808	2.119517	-3.84049
C	-13.0299	-4.96355	0.659892	O	8.921586	4.31141	-0.17745
C	-11.9501	-5.03291	-1.74006	O	11.90357	0.64742	0.625688
C	-9.76629	-3.65813	-2.28392	H	-12.8312	-6.19811	-3.20498
C	-8.62169	-2.16714	-0.43313	H	-8.95541	-3.75262	-4.18026
C	-9.7062	-2.10553	1.987425	H	-8.85393	-0.9768	3.496182
O	-12.996	-3.48541	4.890422	H	-11.9943	-2.39768	6.007439
O	-15.1609	-6.27276	1.31695	H	-15.7437	-7.19816	-0.18028
C	-6.24536	-0.70052	-1.08678	H	-5.56335	-1.36627	-2.9355
C	-4.05308	-1.16539	0.77441	H	-4.459	-0.4182	2.675474
N	-6.67999	2.019739	-1.38366	H	-0.7164	-8.25999	0.367174
O	-3.57196	-3.8437	0.968107	H	3.689879	-8.05704	-1.35701
C	-1.155	-4.21088	0.085794	H	3.142237	0.098455	-2.05772
C	-0.07521	-1.90843	-0.58355	H	6.943232	-5.80788	-3.66116
O	-1.77105	0.022677	-0.13341	H	-7.62221	3.226518	2.417716
C	0.140974	-6.46286	-0.16384	H	-6.00215	2.429243	-5.37325
C	2.603476	-6.31471	-1.1361	H	-7.29642	8.951255	2.060368
C	3.723894	-4.00584	-1.82718	H	-7.88847	10.04389	-1.05503
C	2.342127	-1.72343	-1.53673	H	-12.269	8.338416	-0.8672
C	6.33096	-4.05252	-2.75541	H	-11.7014	7.1477	2.218539
C	-7.36237	3.756965	0.453723	H	10.09737	-2.60177	-3.2012
C	-7.58782	6.052793	-0.76232	C	14.27972	1.944906	0.888738
N	-7.06134	5.75894	-3.30324	C	15.98992	0.281758	2.488391
C	-6.52655	3.34387	-3.60711	H	15.1813	2.231767	-0.96225
C	-8.36884	8.551578	0.31086	H	14.01969	3.763768	1.860435
C	-11.207	8.699166	0.889116	F	16.42626	-1.99196	1.387437
N	-11.8779	11.2382	1.783712	F	15.02294	-0.14778	4.819746
C	8.184782	-2.35082	-2.48631	F	18.25551	1.472853	2.774685
O	7.750712	-0.04687	-1.21642	H	-13.7891	11.32985	2.114226
S	9.961502	2.075675	-1.36325	H	-11.0271	11.56512	3.500907

Total energy = -2351.768610 Ha

Experimental and calculated ECD spectrums of 28

To determine the absolute stereochemistry of isowondonin A (**3**) and B (**4**), the experimental ECD spectrum was compared to the calculated ECD spectrum of **28**. The calculated ECD spectrum of the (1*S*,2*S*)-isomer was in good agreement with the experimental spectrum of **28a** in CH_3OH, and the calculated ECD spectrum of the (1*R*,2*S*)-isomer was in good agreement with the experimental spectrum for **28b**. In addition, the calculated ECD spectra of the (1*R*,2*R*) and (1*S*,2*R*) isomers also matched with the experimental spectra of enantiomers **28a** and **28b**, respectively. Moreover, enantiomer **28a** and **28b** exhibited the opposite profile of both experimental and calculated ECD spectra.

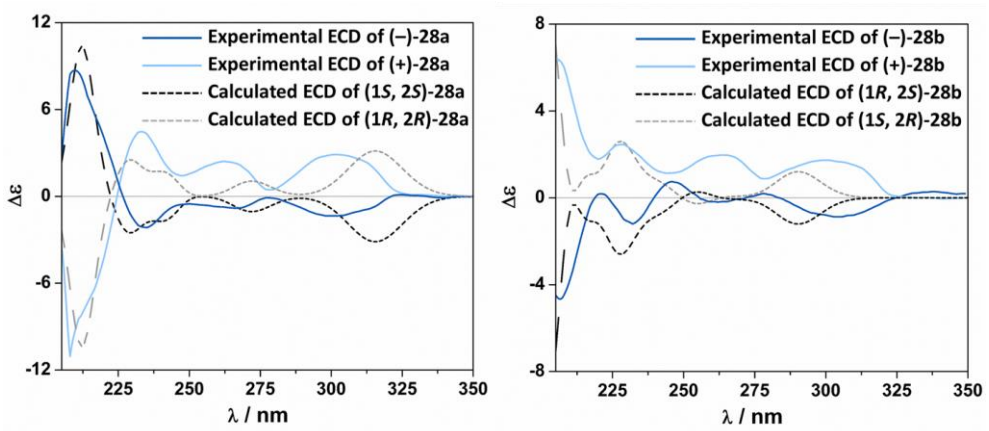


Figure S4. Experimental and calculated ECD spectrums of **28**.

V. Reference

(1) (a) Shin, J.; Rho, J.-R.; Seo, Y.; Lee, H.-S.; Cho, K. W.; Kwon, H. J.; Sim, C. J. *Tetrahedron Lett*. **2001**, *42*, 1965. (b) Chang, Y. H.; Shin, D.; Na, Z.; Lee, H.-S.; Kim, D.-D.; Oh, K. B.; Shin, J. *J. Nat. Prod*. **2008**, *71*, 779.

(2) Jun, H.-O.; Kim, Y.; Kwon, Y.-W.; Hong, S.-S.; Kim, K.-W.; Shin, J.; Kim, T.-Y. *FEBS Lett.* **2007**, *581*, 4977.

(3) (a) Ohta, S.; Kobayashi, H.; Ikegami, S. *Biosci. Biotechnol. Biochem*. **1994**, *58*, 1752. (b) Ohta, S.; Kobayashi, H.; Ikegami, S. *Tetrahedron Lett*. **1994**, *35*, 4579.

(4) (a) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *Tetrahedron Lett*. **1994**, *35*, 5873. (b) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *Tetrahedron* **1994**, *50*, 13583. (c) Musman, M.; Ohtani, I. I.; Nagaoka, D.; Tanaka, J.; Higa, T. *J. Nat. Prod*. **2001**, *64*, 350. (d) Pereira, A. R.; Byrum, T.; Shibuya, G. M.; Vanderwal, C. D.; Gerwick, W. H. *J. Nat. Prod*. **2010**, *73*, 279.

(5) (a) Dagron, F.; Lubineau, A. *J. Carbohydr. Chem*. **2000**, *19*, 311. (b) Zeitouni, J.; Norsikian, S.; Merlet, D.; Lubineau, A. *Adv. Synth. Catal*. **2006**, *348*, 1662. (c) Bedke, D. K.; Shibuya, G. M.; Pereira, A. R.; Gerwick, W. H.; Vanderwal, C. D. *J. Am. Chem. Soc*. **2010**, *132*, 2542.

(6) (a) Ritter, K. *Synthesis* **1993**, 735. (b) Chassaing, S.; Specklin, S.; Weibel, J.-M.; Pale, P. *Curr. Org. Synth.* **2012**, *9*, 806. (c) Chassaing, S.; Specklin, S.; Weibel, J.-M.; Pale, P. *Tetrahedron* **2012**, *68*, 7245.

(7) (a) Proud, A. D.; Prodger, J. C.; Flitsch, S. L. *Tetrahedron Lett*. **1997**, *38*, 7243. (b) Karst, N. A.; Islam, T. F.; Avci, F. Y.; Linhardt, R. J. *Tetrahedron Lett*. **2004**, *45*, 6433. (c) Miller, S. C. *J. Org. Chem*. **2010**, *75*, 4632.

(8) See Supporting Information for details.

(9) Desoky, A. Y.; Hendel, J.; Ingram, L.; Taylor, S. D. *Tetrahedron* **2011**, *67*, 1281.

(10) (a) Baraldi, P. G.; Cacciari, B.; Romagnoli, R.; Spalluto, G.; Monopoli, A.; Ongini, E.; Varani, K.; Borea, P. A. *J. Med. Chem.* **2002**, *45*, 115. (b) Stack, D. E.; Hill, A. L.; Diffendaffer, C. B.; Burns, N. M. *Org. Lett*. **2002**, *4*, 4487. (c) Kim, B.-H.; Lee, J.; Choi, J.-S.; Park, D. Y.; Song, H. Y.; Park, T. K.; Cho, C.-H.; Ye, S.-K.; Joo, C.-K; Koh, G. Y.; Kim, T.-Y. *Br. J. Pharmacol*. **2015**, *172*, 3875.

(11) (a) Appel, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801. (b) de Andrade, V. S. C.; de Mattos, M. C. S. *Curr. Org. Synth.* **2015**, *12*, 309.

(12) Jain, R.; Avramovitch, B.; Cohen, L. A. *Tetrahedron* **1998**, *54*, 3235.

(13) Roy, R. K.; Krishnamurti, S.; Geerlings, P.; Pal, S. *J. Phys. Chem. A* **1998**, *102*, 3746.

(14) Density functional theoretical (DFT) computations were performed using Material studio 2016 and Gaussian 09. See Supporting Information in the computational study section for details.

(15) (a) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem*. **2006**, *4*, 393. (b) Ikariya, T.; Blacker, J. *Acc. Chem. Res*. **2007**, *40*, 1300.

(16) The configuration of C2-OH of **25** was assigned by Mosher analysis. See Supporting Information for details.

(17) (a) Berova, N.; di Bari, L.; Pescitelli, G. *Chem. Soc. Rev*. **2007**, *36*, 914. (b) Nugroho, A. E.; Morita, H. *J. Nat. Med*. **2014**, *68*, 1.

(18) The calculated ECD spectra of the (1*R*,2*R*) and (1*S*,2*R*) isomers were in agreement with the experimental spectra of enantiomers, respectively, which were prepared from **23** using Noyori's (*S*,*S*)-RhTsDPEN catalyst. See Supporting Information for details.

(19) Duynstee, H. I.; de Koning, M. C.; Ovaa, H.; van der Marel, G. A.; van Boom, J. H. *Eur. J. Org. Chem*. **1999**, 2623.

(20) Choi, K. I.; Cha, J. H.; Pae, A. N.; Cho, Y. S.; Kang, H.-Y.; Koh, H. Y.; Chang, M. H. *J. Antibiotics*. **1995**, *48*, 1371.

(21) Yang, W.; Parr, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 6723.

(22) Parr, R. G.; Yang, W. *J. Am. Chem. Soc*. **1984**, *106*, 4049.

(23) Yang, W.; Mortier, W. J. *J. Am. Chem. Soc*. **1986**, *108*, 5708.

(24) Mulliken, R. S. *J. Chem. Phys*. **1955**, *23*, 1833.

(25) (a) Delley, B. *J. Chem. Phys*. **1990**, *92*, 508. (b) Delley, B. *J. Chem. Phys*. **2000**, *113*, 7756.

(26) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett*. **1996**, *77*, 3865.

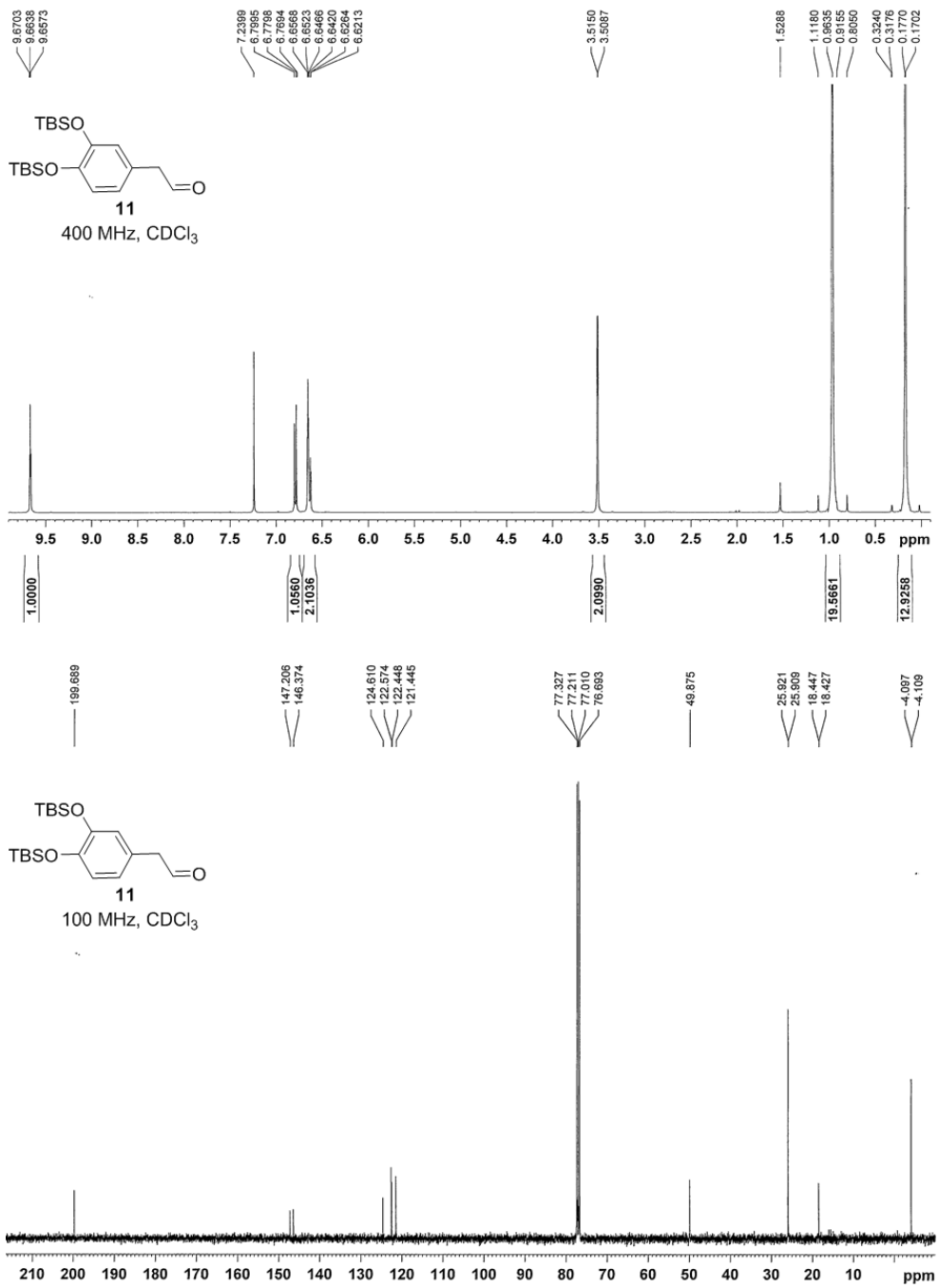
(27) Frisch, M. J.; et al. *Gaussian 09*, Revision B.01; Gaussian: Wallingford, CT, **2009**.

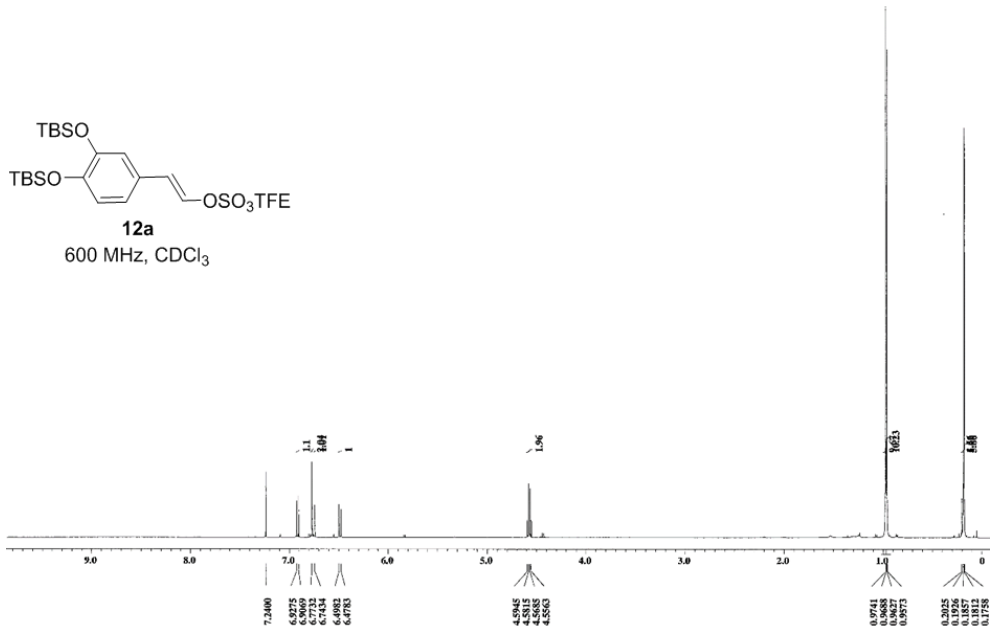
(28) Bruhn, T.; Schaumlӧ ffel, A.; Hemberger, Y.; Bringmann, G. *Chirality* **2013**, *25*, 243.

Appendix

Spectra of Compounds.

^{1}H & ^{13}C NMR Spectrum

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TBSO
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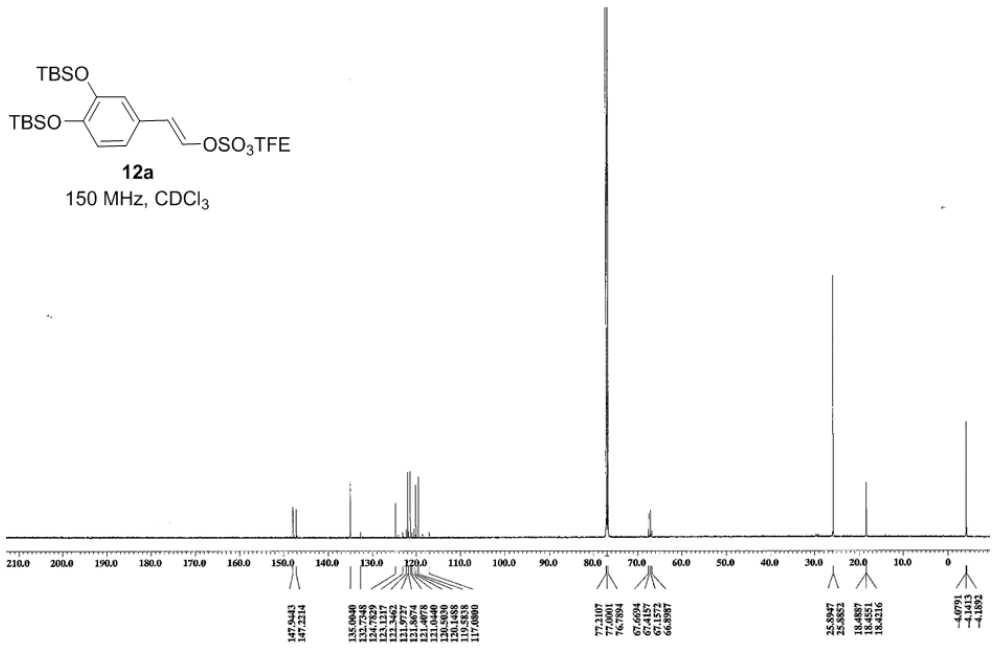
12a
600 MHz, CDCl3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12a
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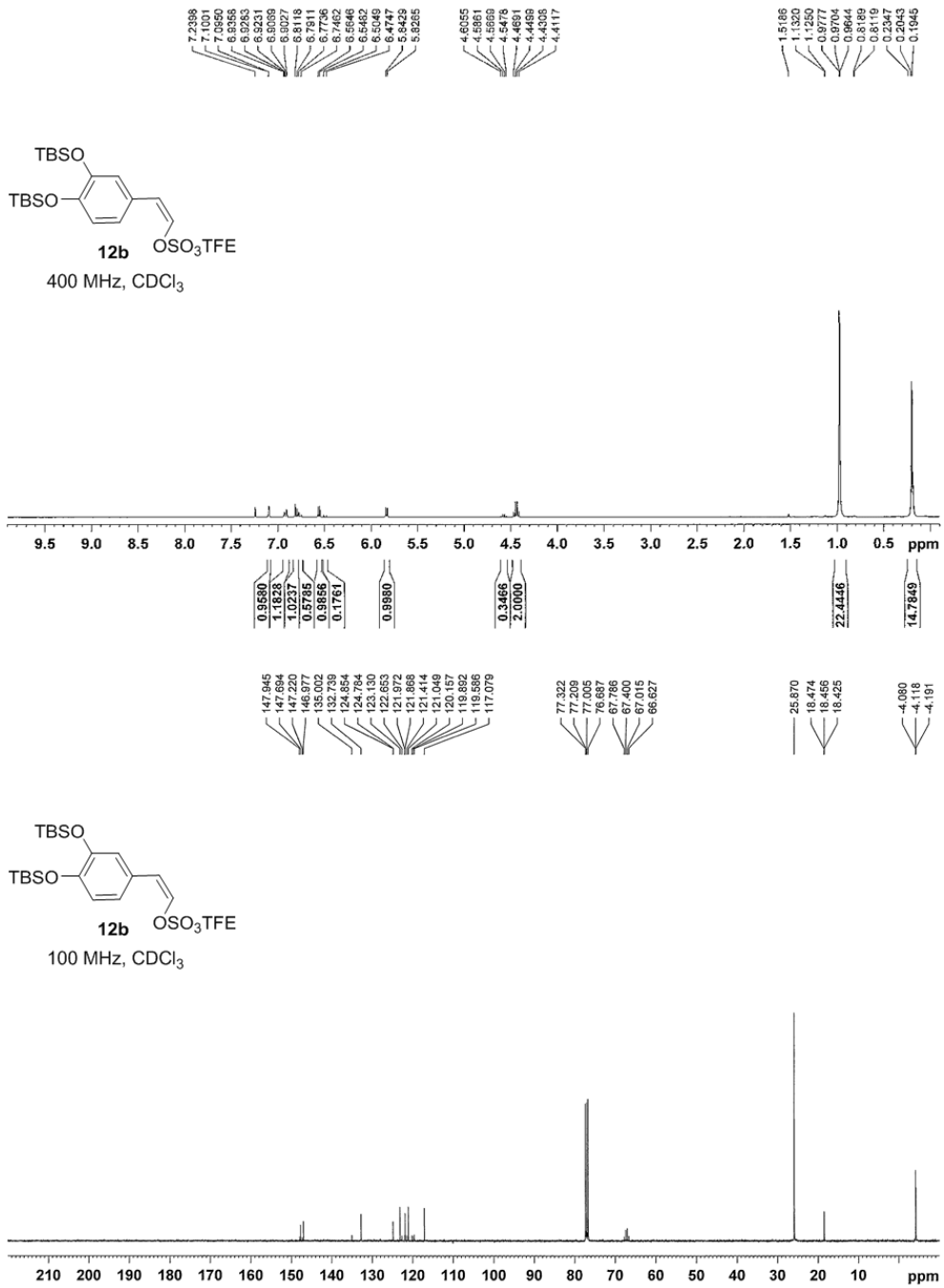
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TBSO
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6.8283
6.8231
6.8059
6.8027
6.8118
6.7911
6.7736
6.7462
6.6446
6.6462
6.6349
6.4447
5.8429
5.8265
4.6055
4.5861
4.5669
4.5478
4.4691
4.4499
4.4308
4.4117
1.5186
1.1320
1.1250
0.9777
0.9704
0.9644
0.8189
0.8119
0.2347
0.2043
0.1945
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.9580
1.1828
1.0237
0.5785
0.9856
0.1761
0.9980
0.3466
2.0000
22.4446
14.7849
147.945
147.694
147.220
146.977
135.002
132.739
124.854
124.784
123.130
122.653
121.972
121.866
121.414
121.049
120.157
119.892
119.586
117.079
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77.209
77.005
76.687
67.786
67.400
67.015
66.627
25.870
18.474
18.456
18.425
-4.080
-4.118
-4.191
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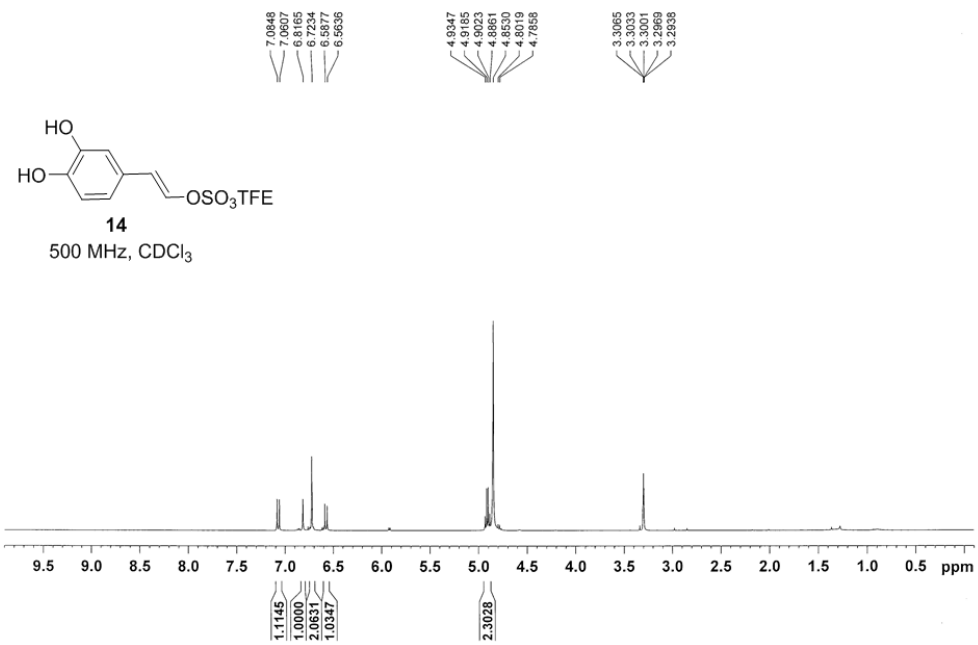
TBSO
OSO3TFE
12b
100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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3.3001
3.2969
3.2938
HO
HO
OSO3TFE
14
500 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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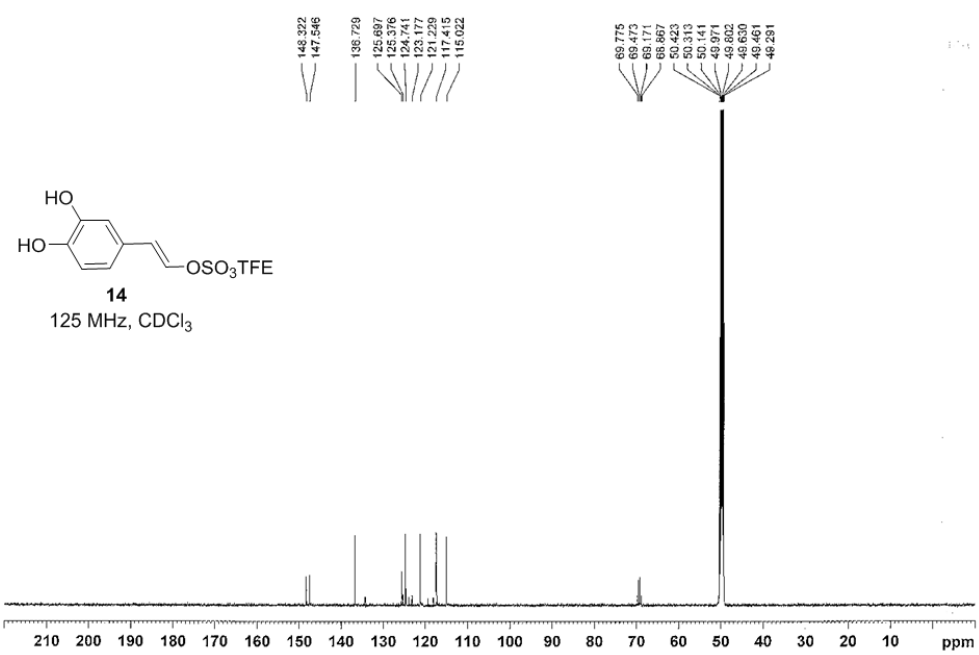
1.0347
2.3028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68.867
50.423
50.313
50.141
49.971
49.822
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49.461
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HO
HO
OSO3TFE
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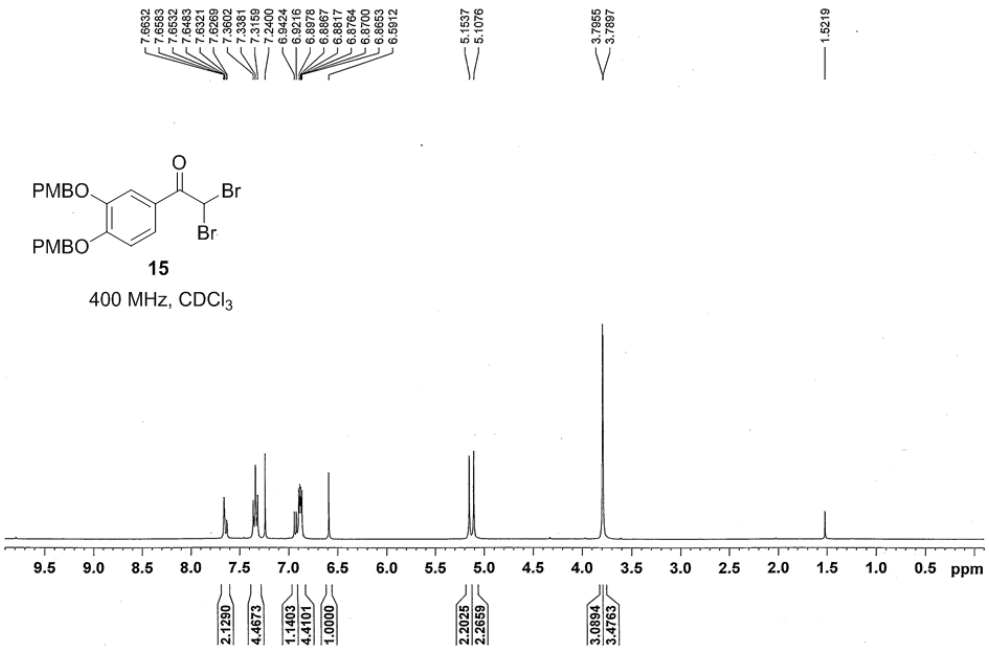
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6.8764
6.8700
6.8653
6.5912
5.1537
5.1076
3.7955
3.7897
1.5219
PMBO
PMBO
O
Br
Br
15
400 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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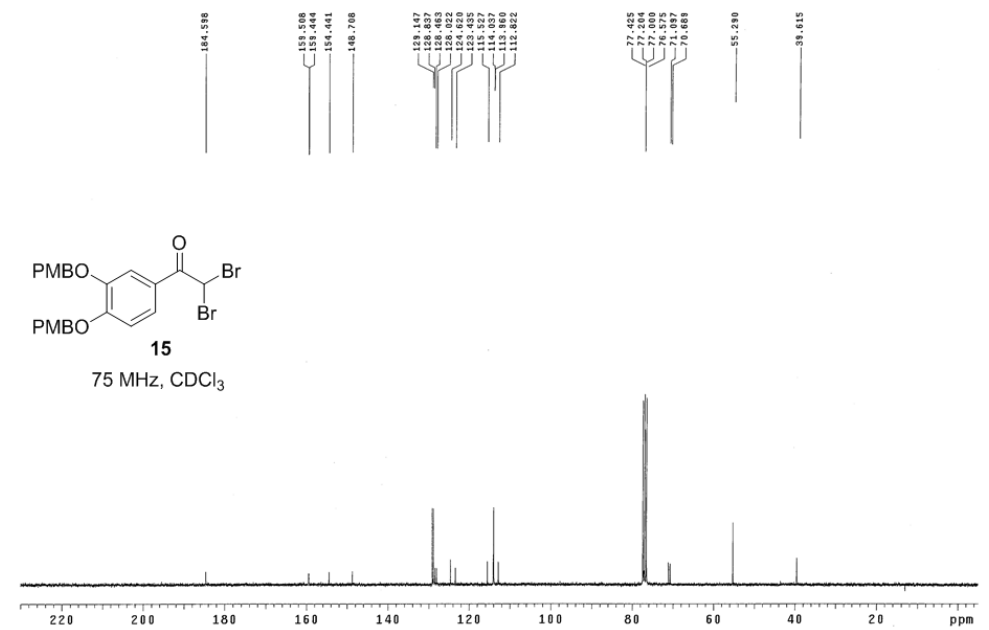
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113.860
112.822
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77.204
77.000
76.575
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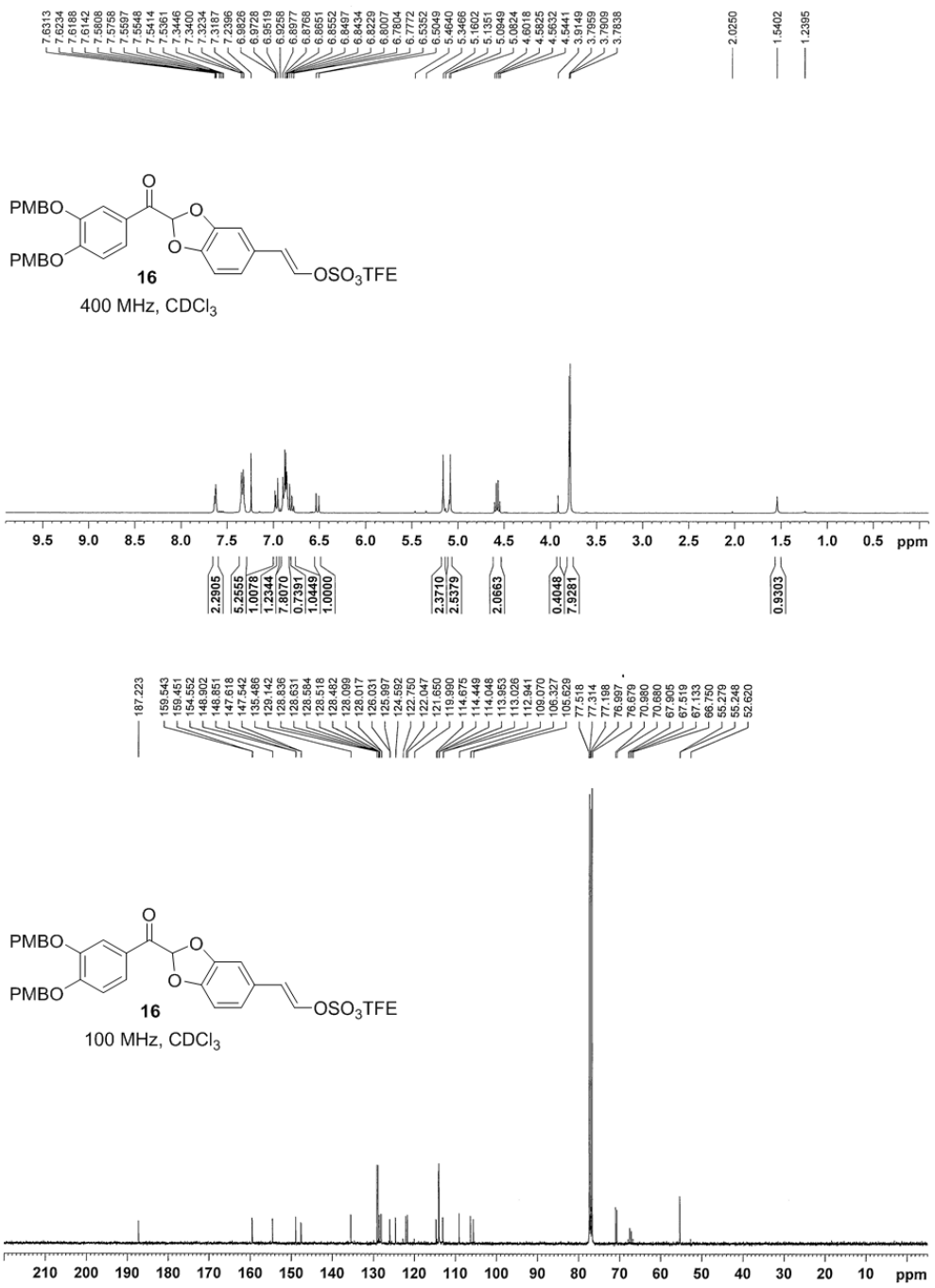
PMBO
PMBO
O
Br
Br
15
75 MHz, CDCl3
220 200 180 160 140 120 100 80 60 40 20 ppm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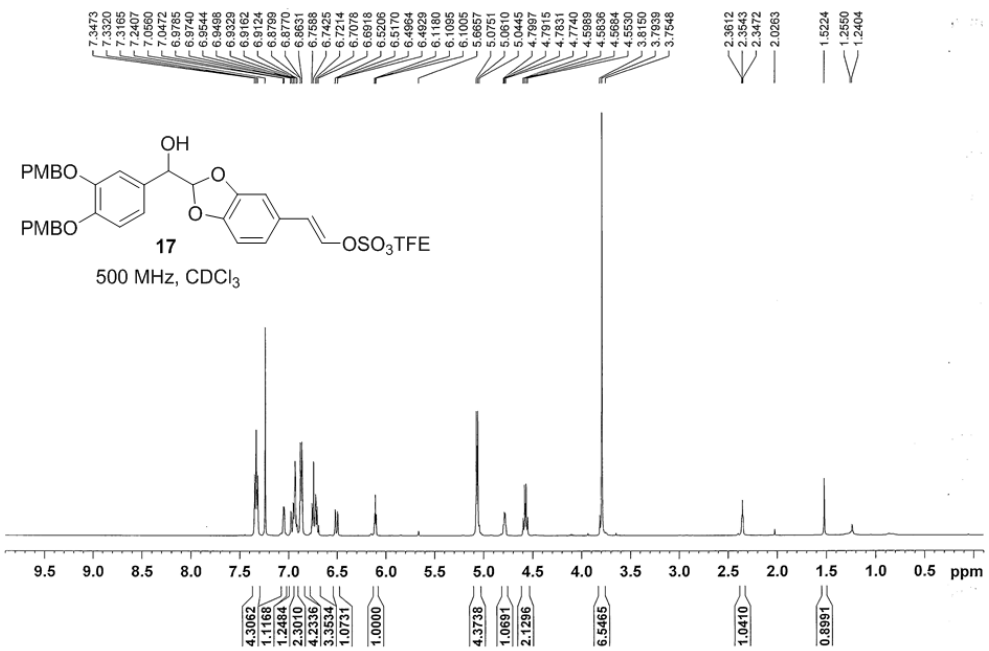
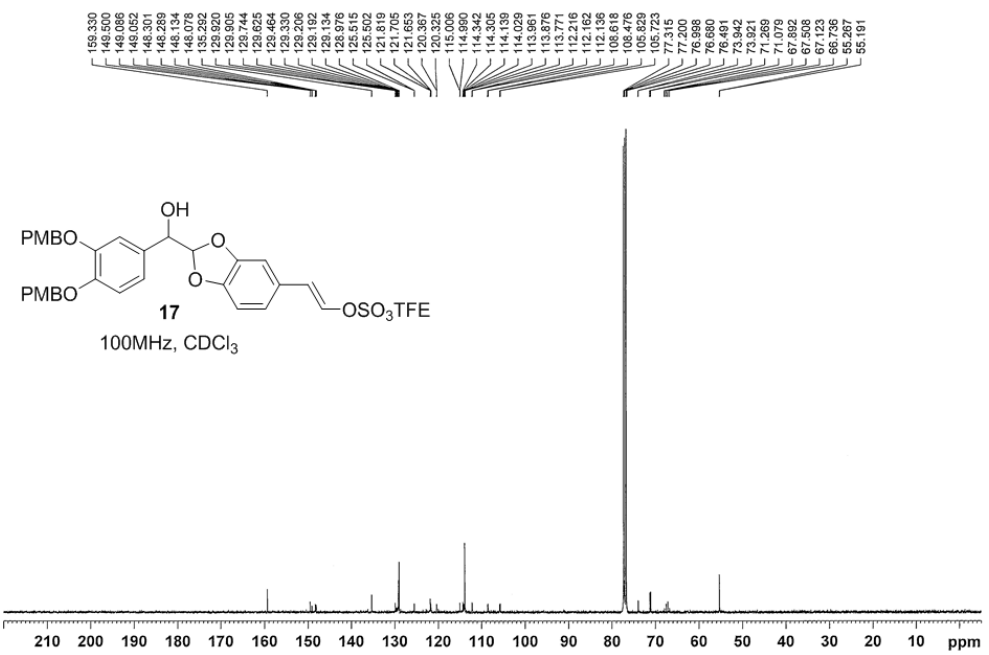
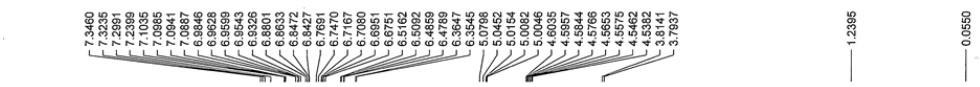
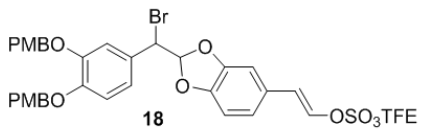
3.7959
3.7909
3.7838
2.0250
1.5402
1.2395
PMBO
PMBO
O
O
O
OSO3TFE
16
400 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.2905
5.2555
1.0078
1.2344
7.8070
0.7391
1.0449
1.0000
2.3710
2.5379
2.0663
0.4048
7.9281
0.9303
187.223
159.543
159.451
154.552
148.902
148.851
147.618
147.542
135.486
129.142
128.836
128.631
128.584
128.518
128.482
128.099
128.017
128.031
123.997
124.582
122.760
122.047
121.650
119.690
114.675
114.449
114.048
113.953
113.026
112.941
109.070
106.327
105.629
77.518
77.314
77.198
76.997
76.679
70.980
70.880
67.905
67.519
67.133
66.750
55.279
55.248
52.620
PMBO
PMBO
O
O
O
OSO3TFE
16
100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.3473
7.3320
7.3165
7.2407
7.0560
7.0472
6.9785
6.9740
6.9544
6.9498
6.9329
6.9162
6.9124
6.8799
6.8770
6.8631
6.7588
6.7425
6.7214
6.7078
6.6918
6.5206
6.5170
6.4964
6.4929
6.1160
6.1095
6.1005
5.6657
5.0751
5.0510
5.0445
4.7997
4.7915
4.7751
4.7740
4.5988
4.5838
4.5684
4.5530
3.8150
3.7939
3.7548
2.3612
2.3543
2.3472
2.0263
1.5224
1.2550
1.2404
OH
PMBO
PMBO
O
O
OSO3TFE
17
500 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.3062
1.1168
1.2484
2.3010
4.2336
3.3534
1.0731
1.0000
4.3738
1.0691
2.1296
5.5465
1.0410
0.8991

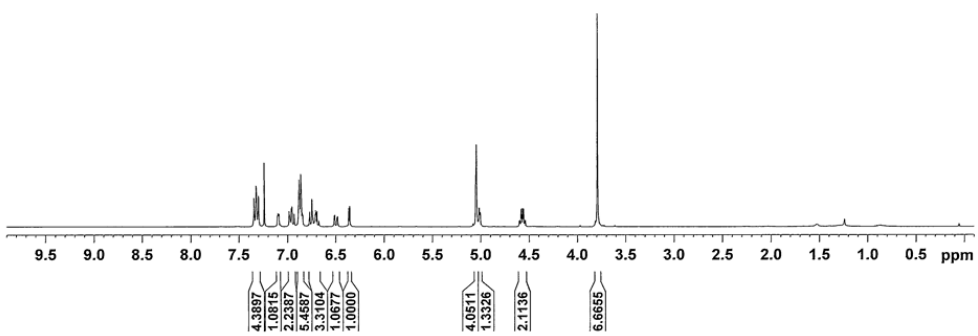

159.330
149.500
149.086
149.052
148.301
148.289
148.134
148.078
135.292
129.920
129.905
129.744
129.625
129.464
129.330
129.206
129.192
129.134
128.976
125.515
125.502
121.819
121.705
121.653
120.367
120.325
115.006
114.990
114.342
114.305
114.138
114.029
113.961
113.876
113.771
112.216
112.162
112.135
108.618
108.475
105.829
105.723
77.315
77.200
76.998
76.680
76.491
73.942
73.921
71.269
71.079
67.892
67.508
67.123
66.736
55.267
55.191
OH
PMBO
PMBO
O
O
OSO3TFE
17
100MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

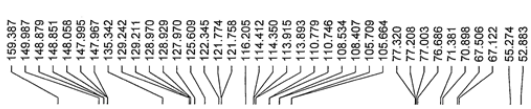


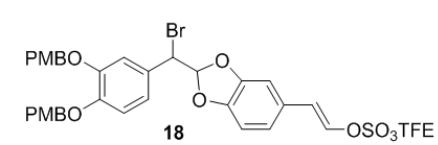


18

400 MHz, $CDCl_3$

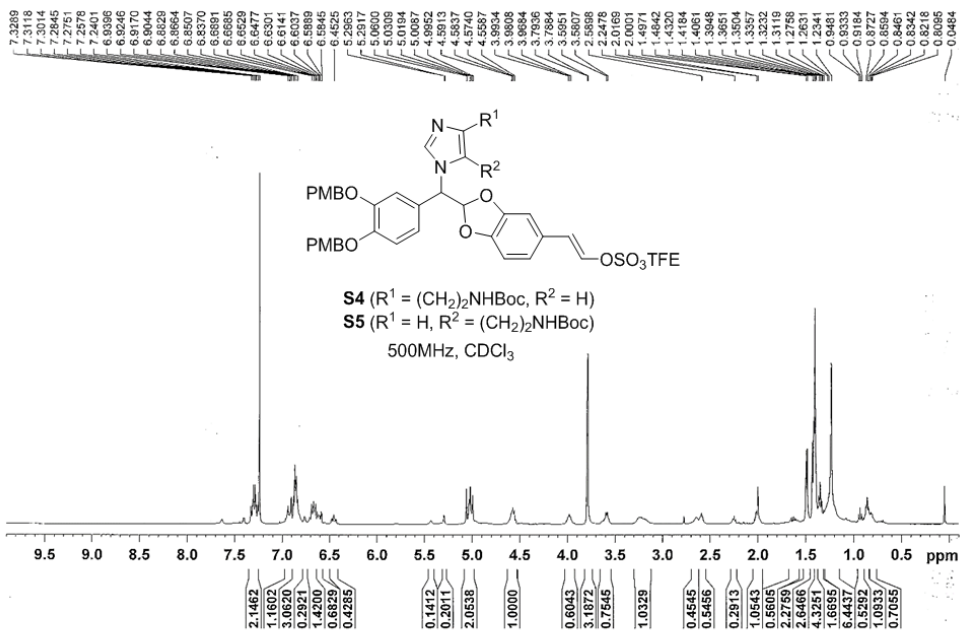


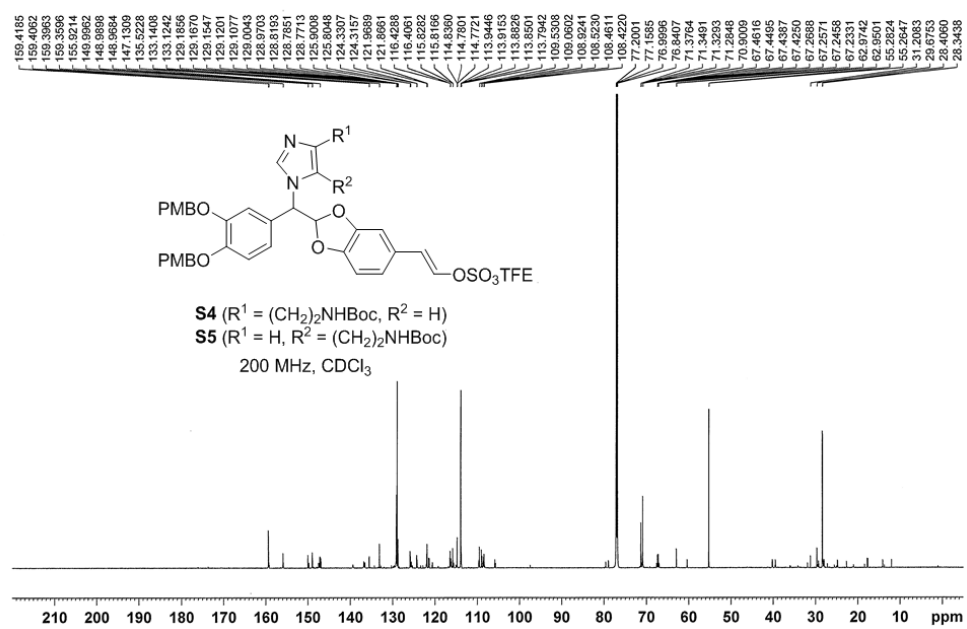


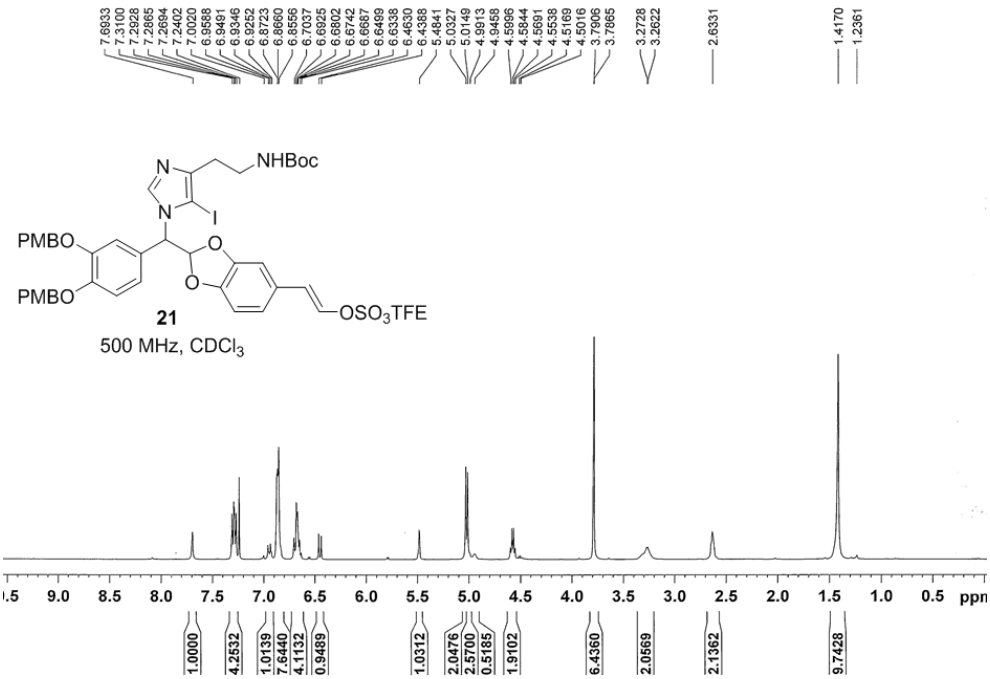


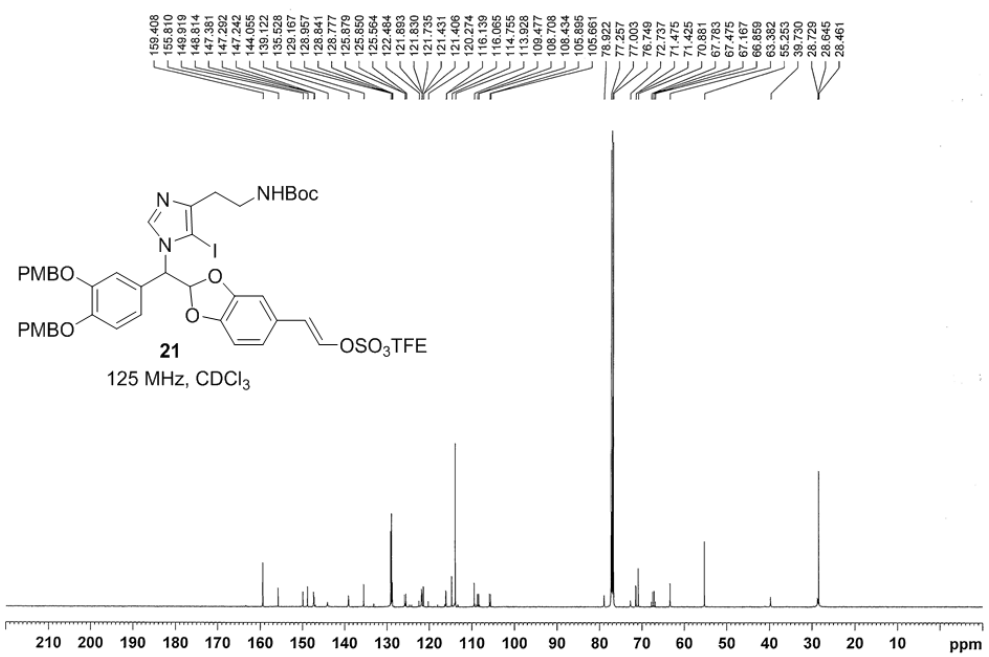
18

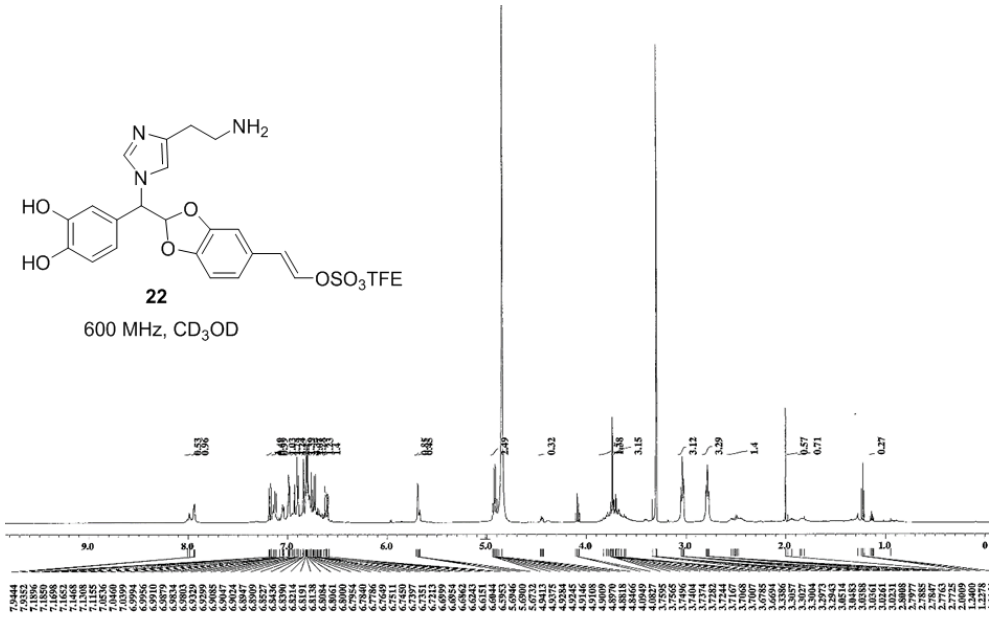
100 MHz, $CDCl_3$


PMBO
PMBO
OSO3TFE
S4 (R1 = (CH2)2NHBoc, R2 = H)
S5 (R1 = H, R2 = (CH2)2NHBoc)
500MHz, CDCl3
ppm


PMBO
PMBO
OSO3TFE
S4 (R1 = (CH2)2NHBoc, R2 = H)
S5 (R1 = H, R2 = (CH2)2NHBoc)
200 MHz, CDCl3
ppm


7.6933
7.3100
7.2928
7.2865
7.2684
7.2402
7.0020
6.9588
6.9491
6.9346
6.9252
6.8723
6.8660
6.8556
6.7037
6.6925
6.6802
6.5742
6.5687
6.5499
6.5338
6.4630
6.4388
5.4841
5.0327
5.0149
4.9913
4.9458
4.5996
4.5844
4.5691
4.5538
4.5169
4.5016
3.7906
3.7865
3.2728
3.2622
2.6331
1.4170
1.2361
NHBoc
N
N
I
PMBO
PMBO
O
O
OSO3TFE
21
500 MHz, CDCl3
1.0000
4.2532
1.0139
7.6440
4.1132
0.9489
1.0312
2.0476
2.5700
0.5185
1.9102
6.4360
2.0569
2.1362
9.7428
ppm


159.408
155.610
149.019
148.814
147.381
147.292
147.242
144.055
139.122
135.528
129.167
128.957
128.841
128.777
125.879
125.850
125.564
122.484
121.893
121.830
121.735
121.431
121.406
120.274
116.139
116.065
114.755
113.928
109.477
108.708
108.434
105.895
105.661
78.922
77.257
77.003
76.749
72.737
71.475
71.425
70.881
67.783
67.475
67.167
66.859
63.382
55.253
39.730
28.728
28.645
28.461
NHBoc
N
N
I
PMBO
PMBO
O
O
OSO3TFE
21
125 MHz, CDCl3
ppm

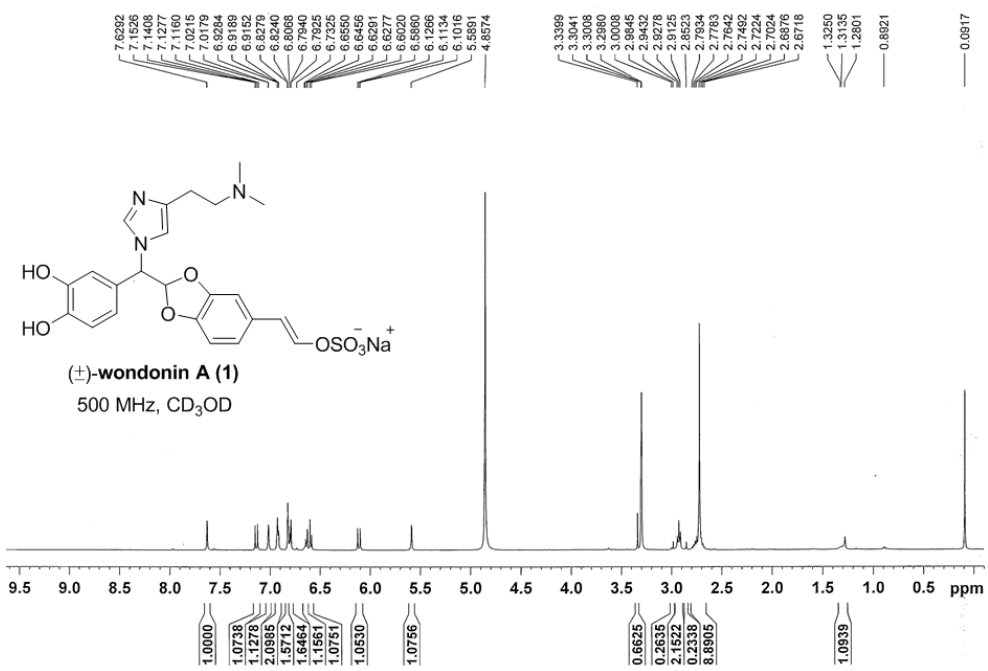


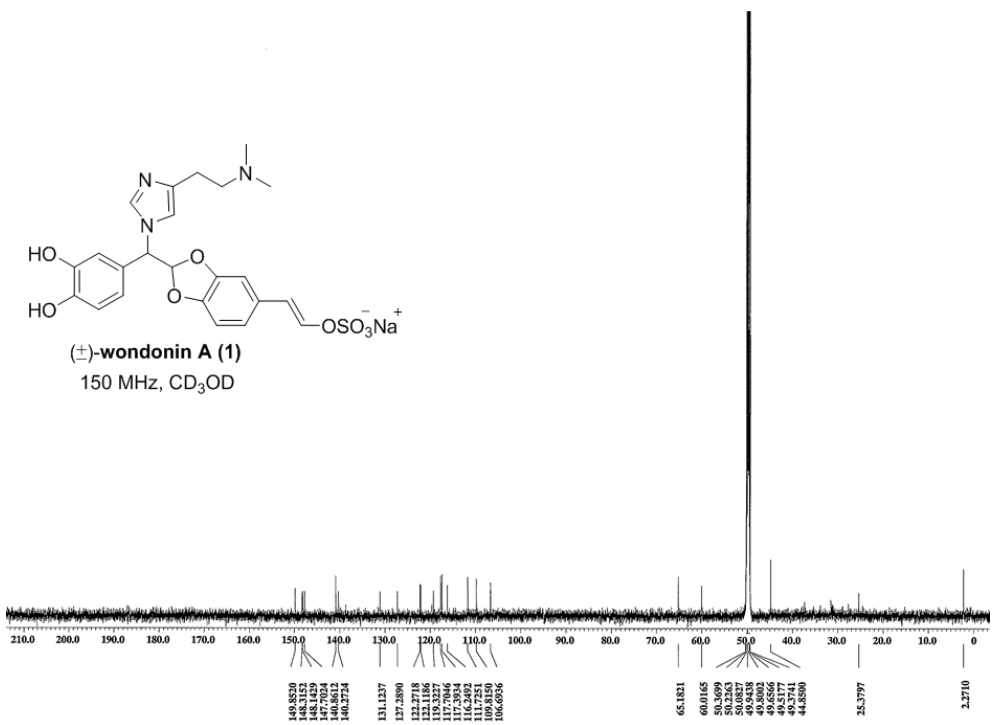
22

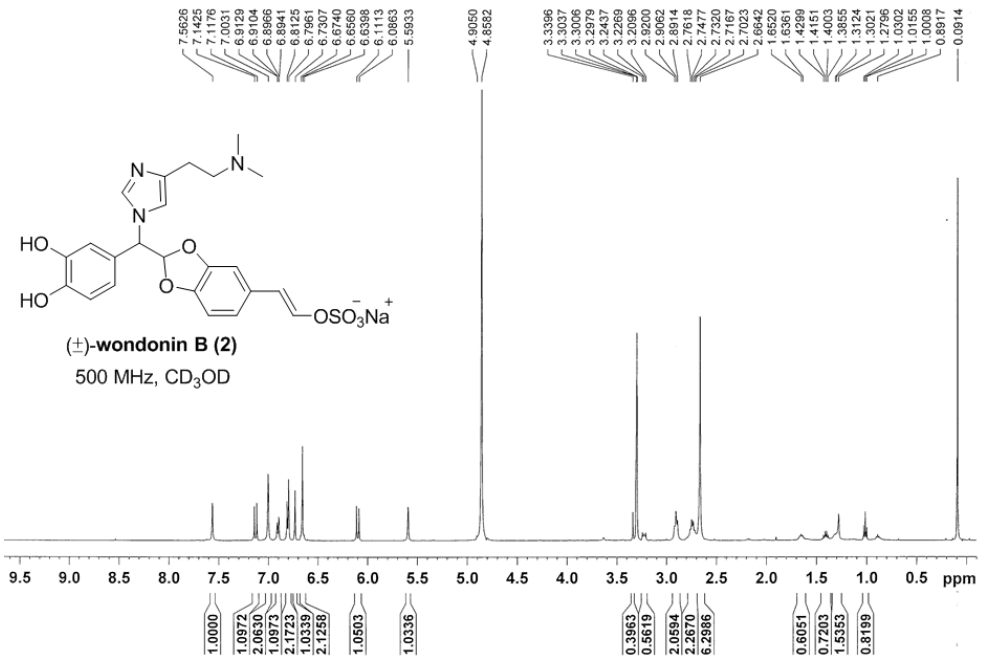
600 MHz, CD_3OD

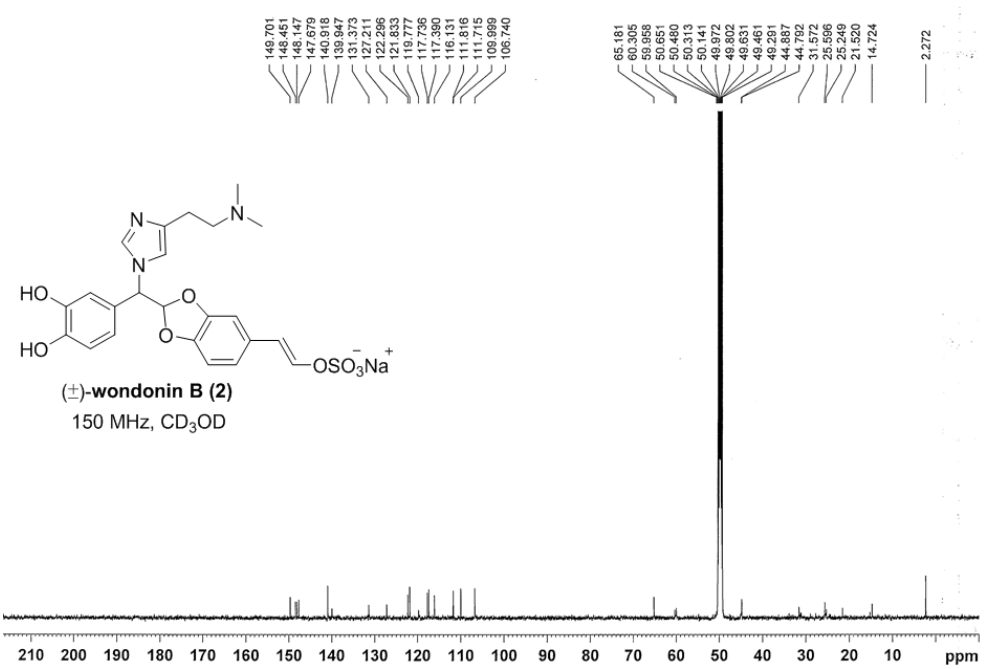
22

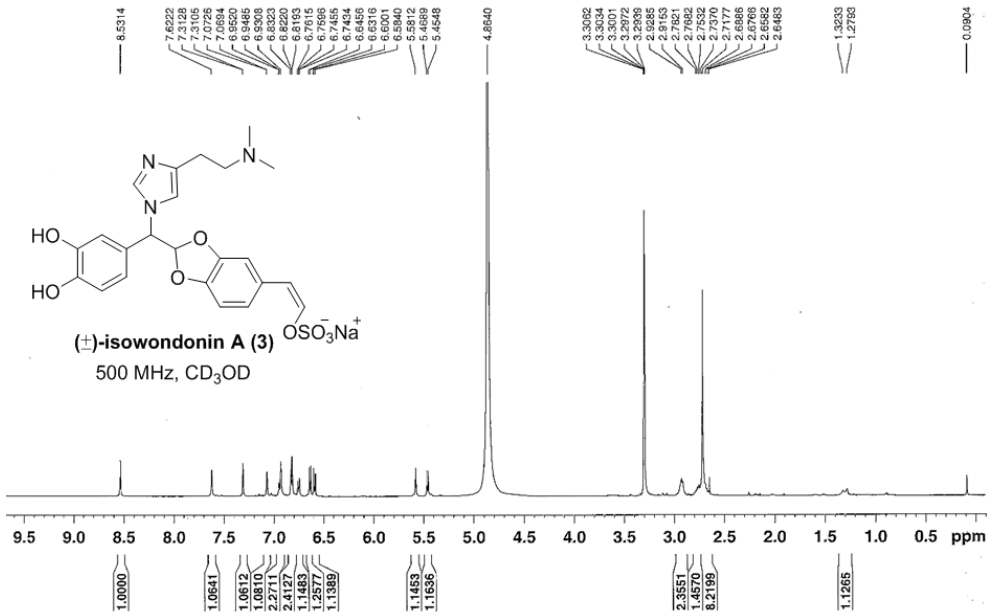
150 MHz, CD_3OD

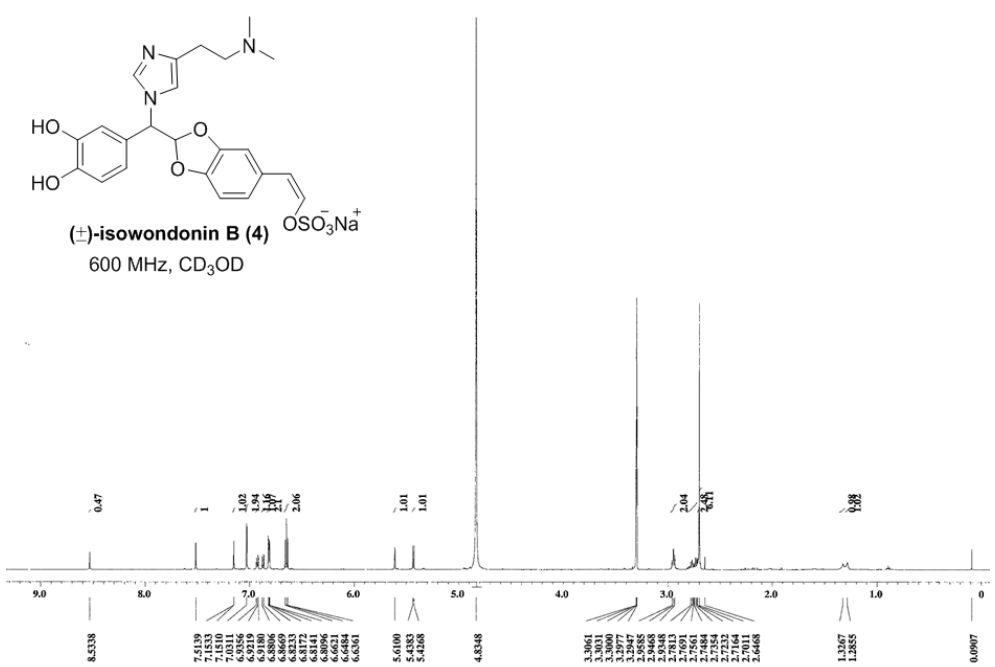

(±)-wondonin A (1)
500 MHz, CD3OD

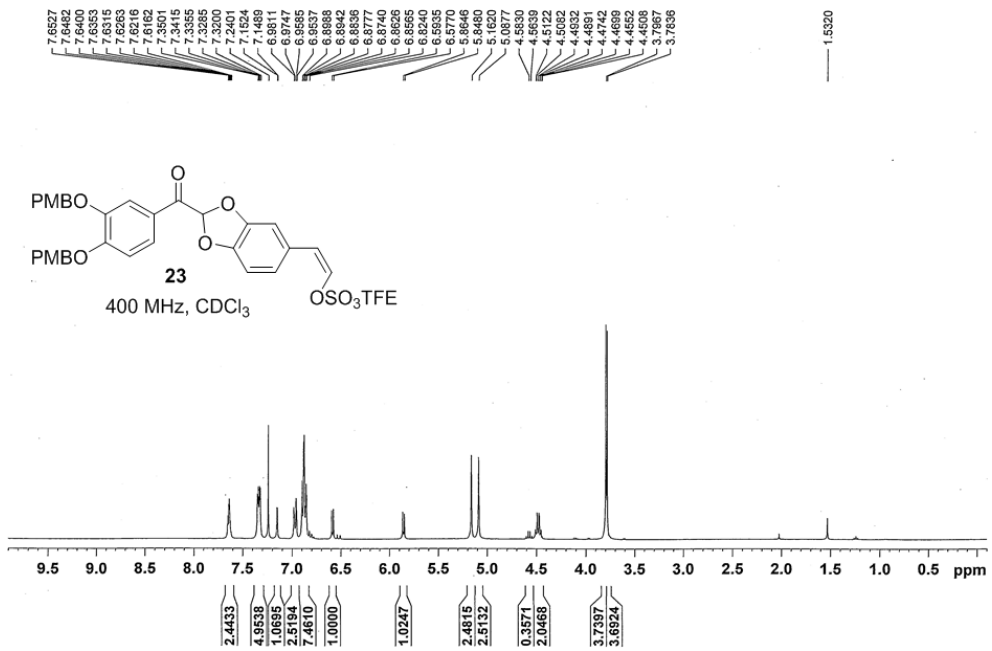

(±)-wondonin A (1)
150 MHz, CD3OD

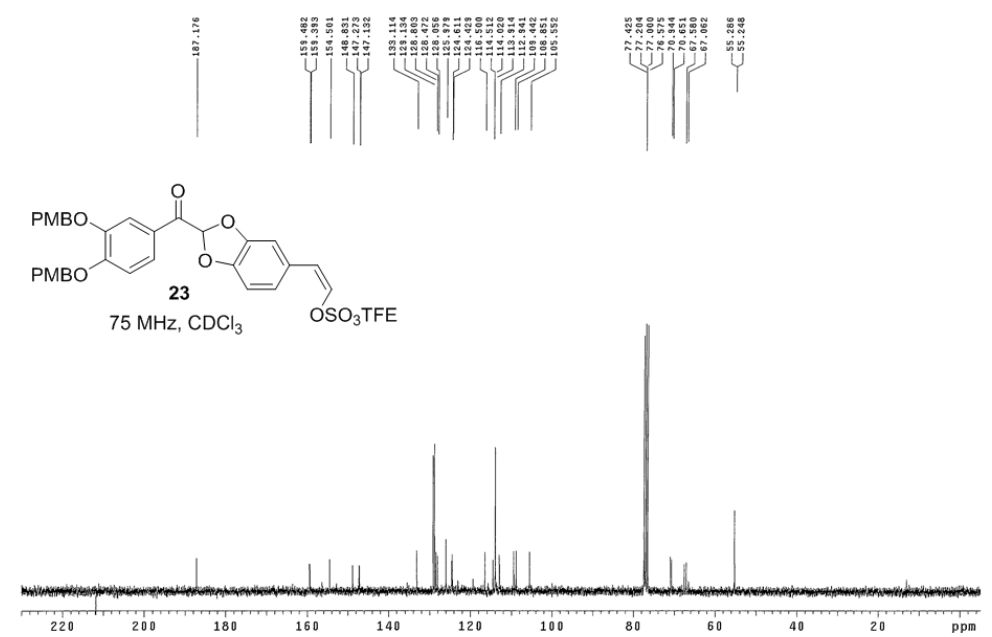

(±)-wondonin B (2)
500 MHz, CD3OD

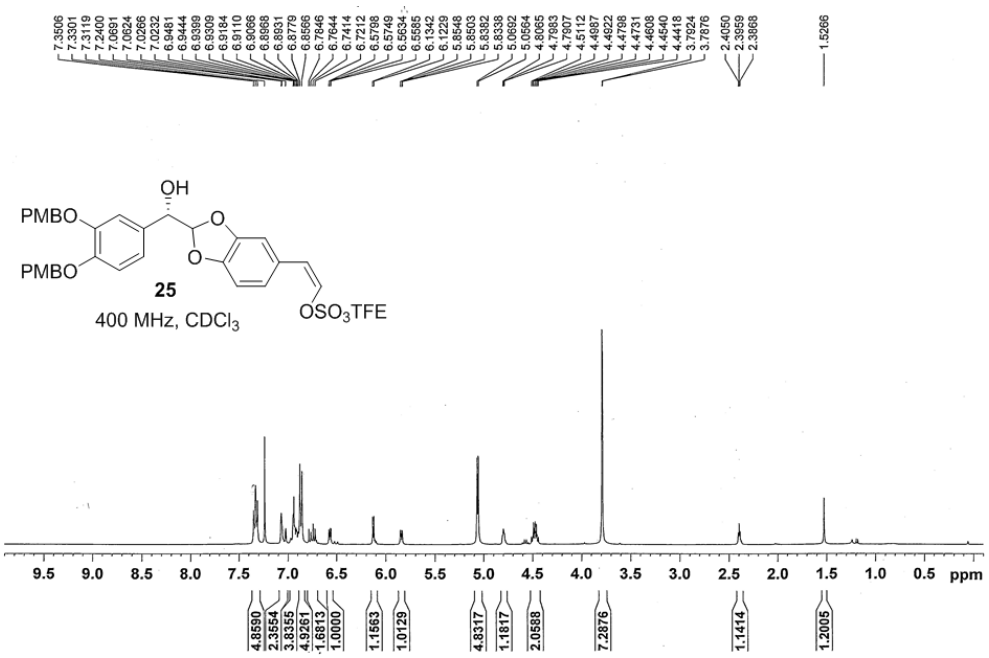

(±)-wondonin B (2)
150 MHz, CD3OD

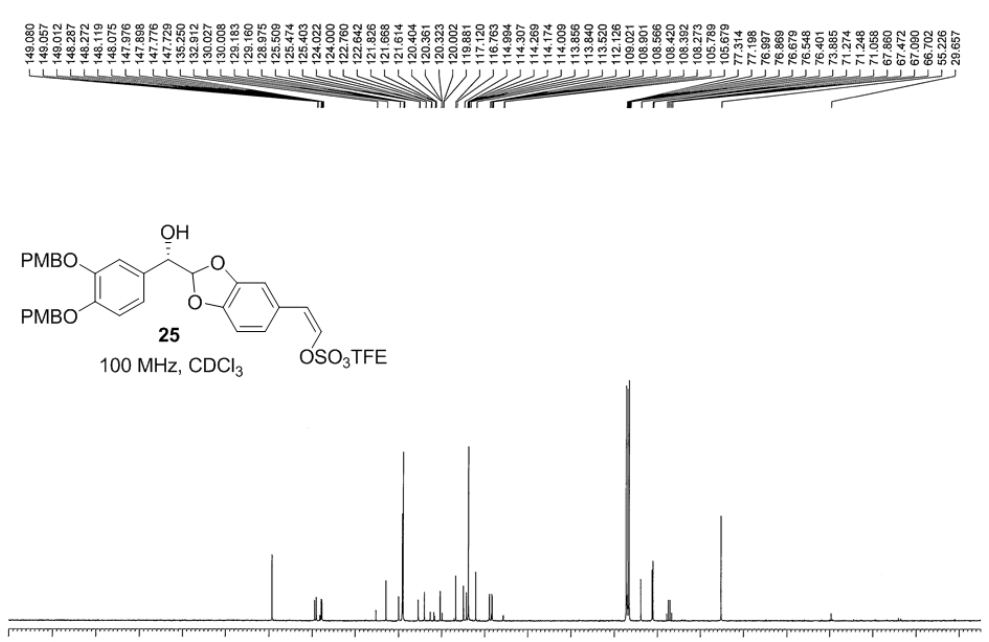

(±)-isowondonin A (3)
500 MHz, CD3OD

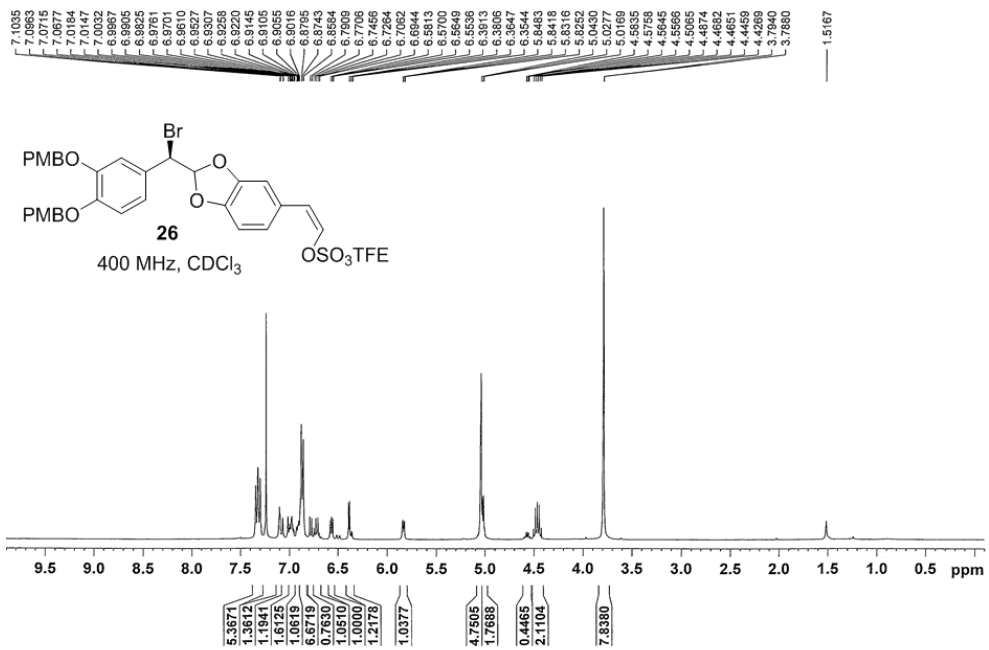

(±)-isowondonin B (4)
600 MHz, CD3OD

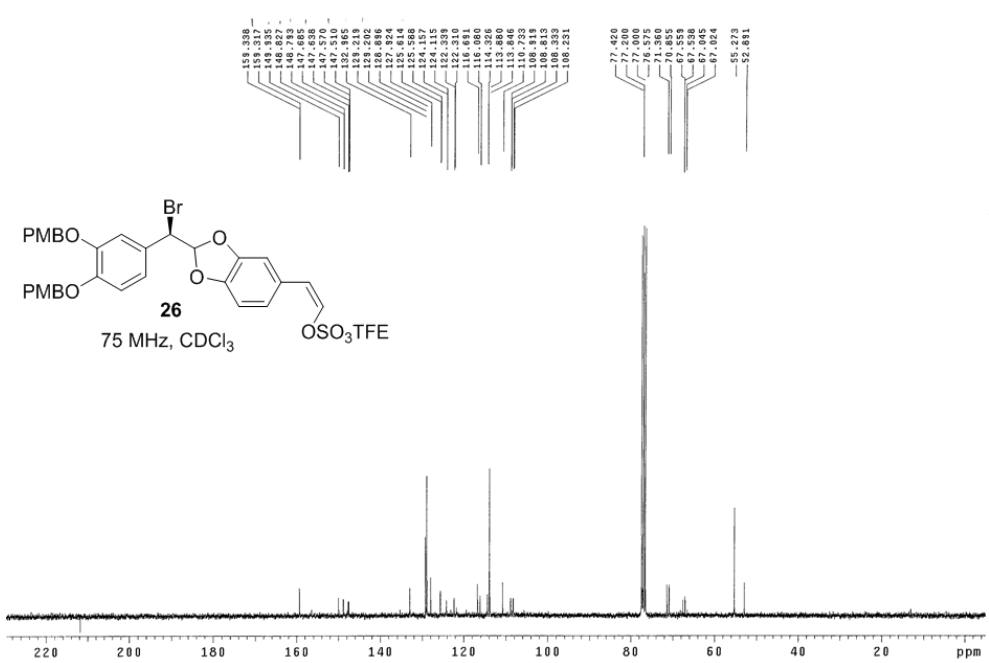

7.6527
7.6482
7.6400
7.6353
7.6315
7.6263
7.6216
7.6162
7.3501
7.3415
7.3355
7.3285
7.3200
7.2401
7.1524
7.1469
6.9811
6.9747
6.9585
6.9537
6.8868
6.8842
6.8636
6.8777
6.8740
6.8628
6.8555
6.8240
6.8035
6.5770
5.8646
5.8480
5.1620
5.0877
4.5830
4.5639
4.5122
4.5062
4.4893
4.4742
4.4699
4.4552
4.4508
3.7967
3.7836
1.5320
PMBO
PMBO
O
O
O
23
OSO3TFE
400 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.4433
4.9538
1.0695
2.5194
7.4610
1.0000
1.0247
2.4815
2.5132
0.3571
2.0468
3.7397
3.6924

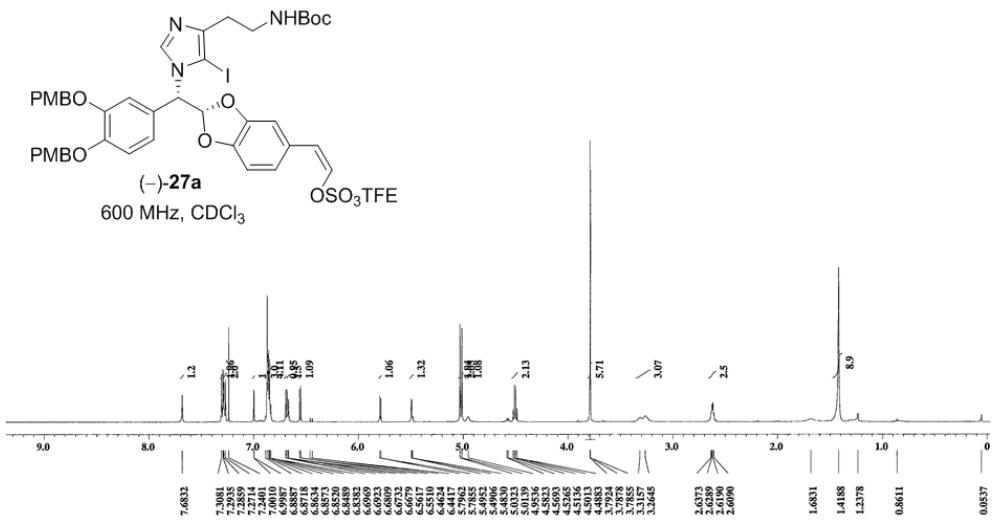

187.176
159.482
159.393
154.501
148.831
147.273
147.192
133.114
129.134
128.803
128.472
128.056
125.379
124.611
124.428
115.590
114.512
114.020
113.914
113.441
108.466
108.851
105.592
77.425
77.204
77.000
76.575
70.344
70.651
67.580
67.062
55.286
55.248
PMBO
PMBO
O
O
O
23
OSO3TFE
75 MHz, CDCl3
220 200 180 160 140 120 100 80 60 40 20 ppm

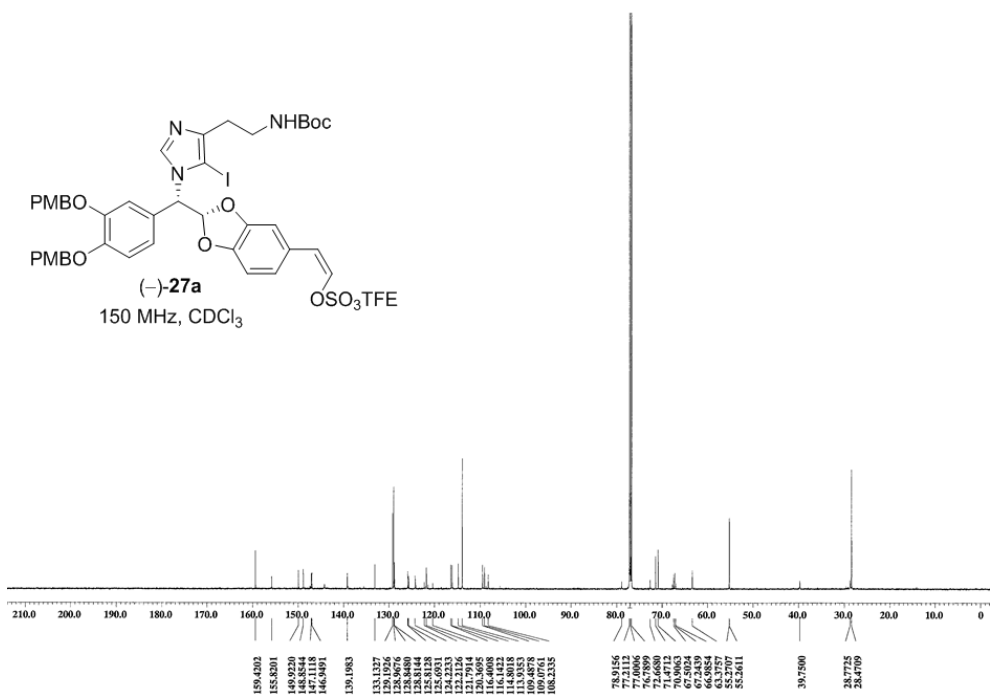

7.3506
7.3301
7.3119
7.2400
7.0691
7.0624
7.0266
7.0232
6.9461
6.9444
6.9369
6.9309
6.9184
6.9110
6.9066
6.8968
6.8931
6.8779
6.8566
6.7846
6.7644
6.7414
6.7212
6.5798
6.5749
6.5634
6.5585
6.1342
6.1229
5.8546
5.8503
5.8382
5.8338
5.0692
5.0564
4.8065
4.7983
4.7907
4.5112
4.4687
4.4622
4.4798
4.4731
4.4608
4.4540
4.4418
3.7924
3.7876
2.4050
2.3859
2.3868
1.5266
OH
PMBO
PMBO
O
O
25
OSO3TFE
400 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.8590
2.3554
3.8355
4.9261
1.6813
1.0000
1.1563
1.0129
4.8317
1.1817
2.0588
7.2876
1.1414
1.2005

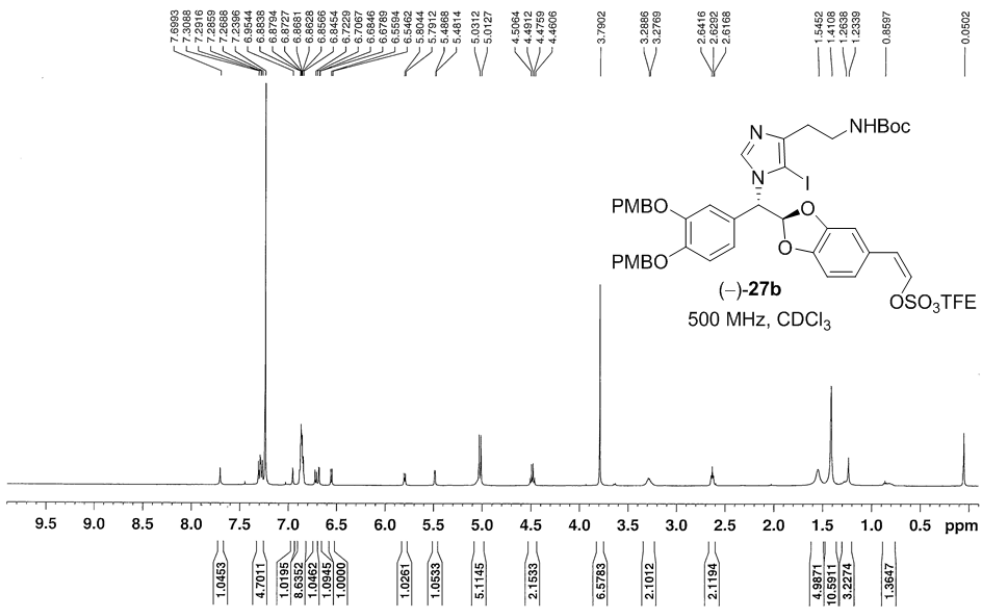

149.080
149.057
149.012
148.287
148.272
148.119
148.075
147.976
147.898
147.776
147.729
135.250
132.912
130.027
130.008
129.183
129.160
128.975
125.509
125.474
125.403
124.022
124.000
122.760
122.642
121.826
121.668
121.614
120.404
120.361
120.323
120.002
119.881
117.120
116.763
114.994
114.307
114.269
114.174
114.009
113.856
113.840
113.520
112.126
109.021
108.901
108.566
108.420
108.392
108.273
105.789
105.679
77.314
77.198
76.997
76.869
76.679
76.548
76.401
73.885
71.274
71.248
71.058
67.860
67.472
67.090
66.702
55.226
29.657
OH
PMBO
PMBO
O
O
25
OSO3TFE
100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

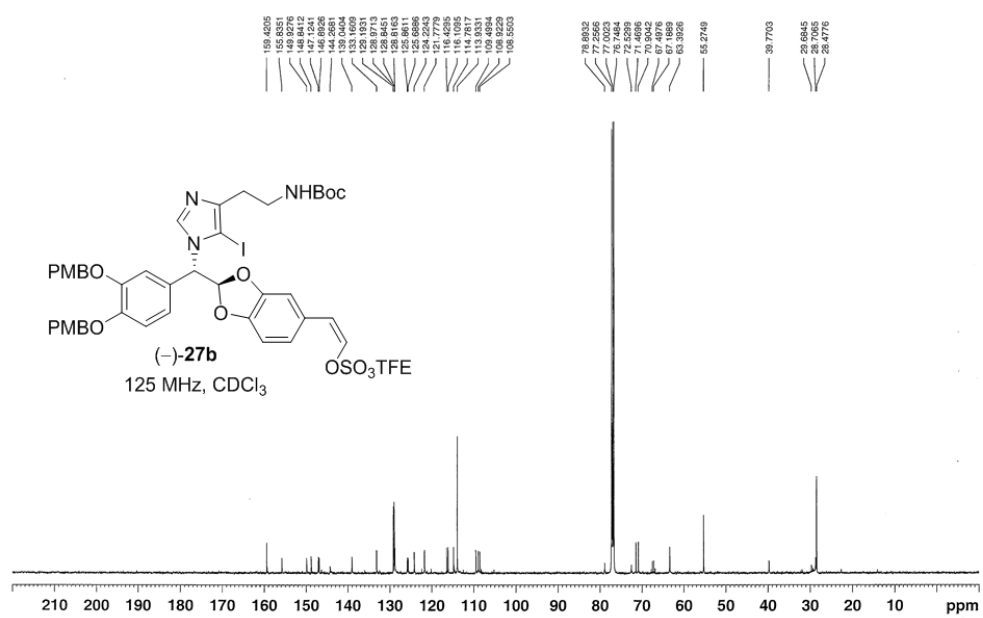

PMBO
PMBO
Br
O
O
O
OSO3TFE
26
400 MHz, CDCl3
ppm

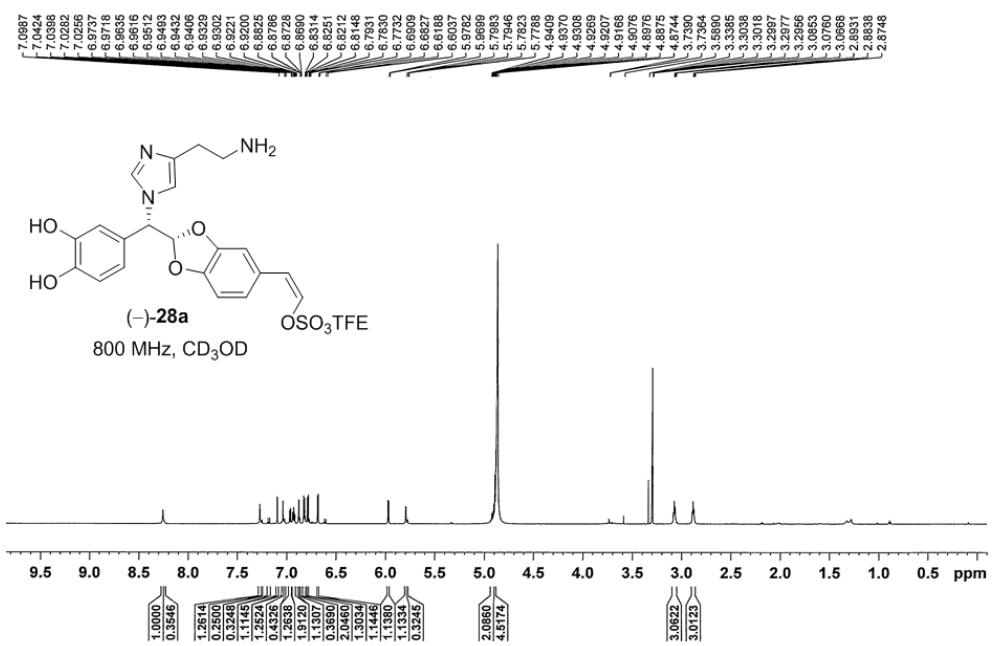

PMBO
PMBO
Br
O
O
O
OSO3TFE
26
75 MHz, CDCl3
ppm

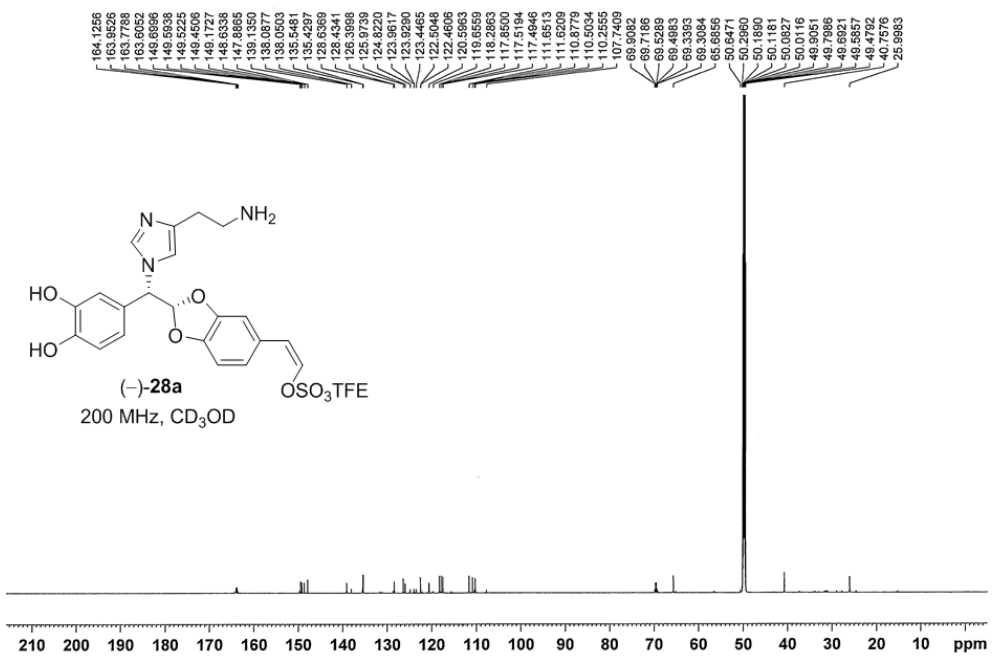

NHBoc
N
N
I
PMBO
PMBO
O
O
OSO3TFE
(–)-27a
600 MHz, CDCl3

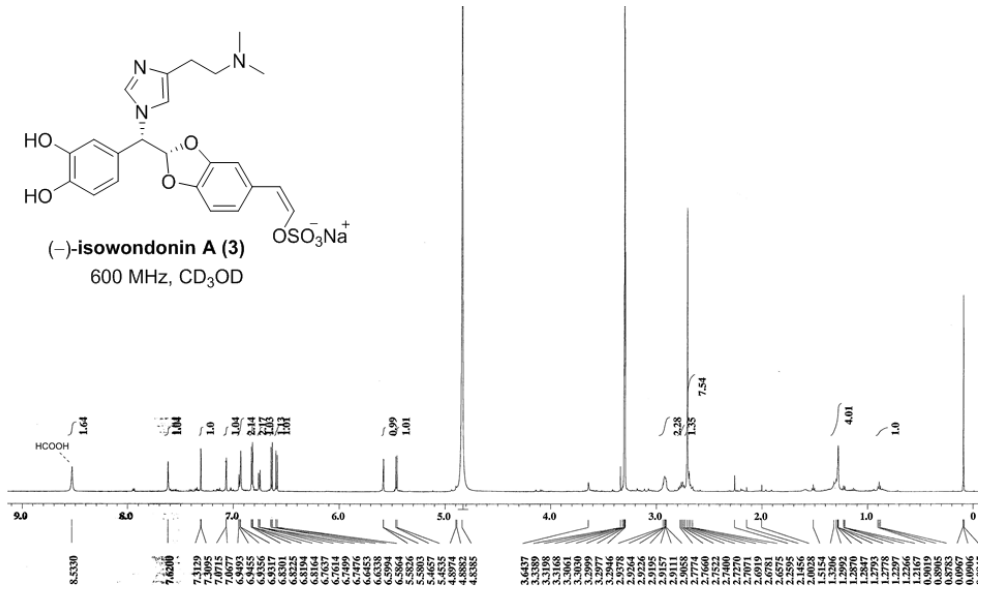

NHBoc
N
N
I
PMBO
PMBO
O
O
OSO3TFE
(–)-27a
150 MHz, CDCl3

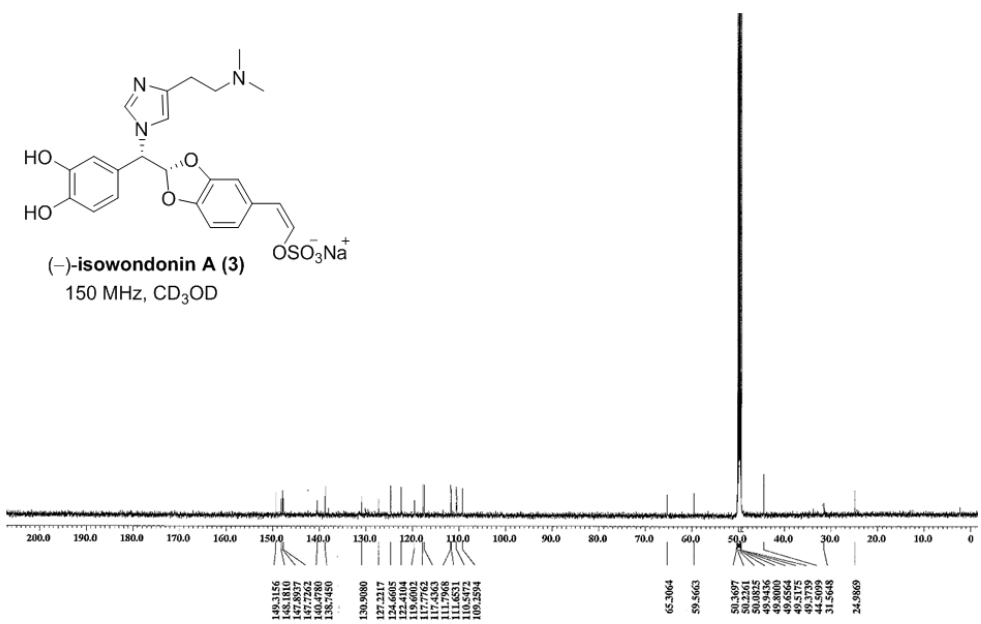

NHBoc
PMBO
PMBO
OSO3TFE
(−)-27b
500 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

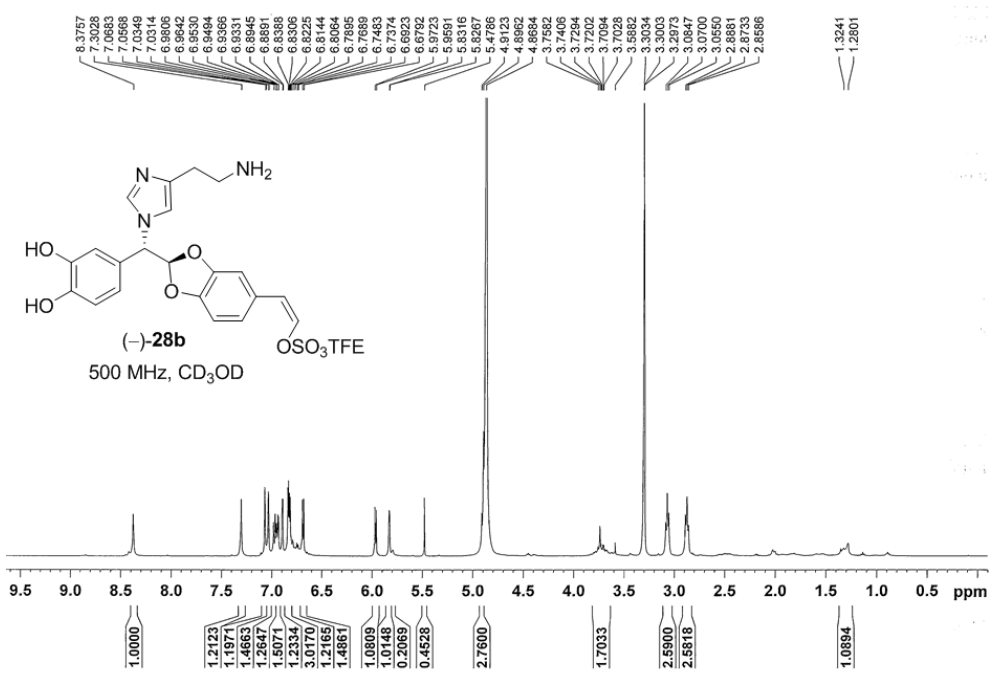

NHBoc
PMBO
PMBO
OSO3TFE
(−)-27b
125 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

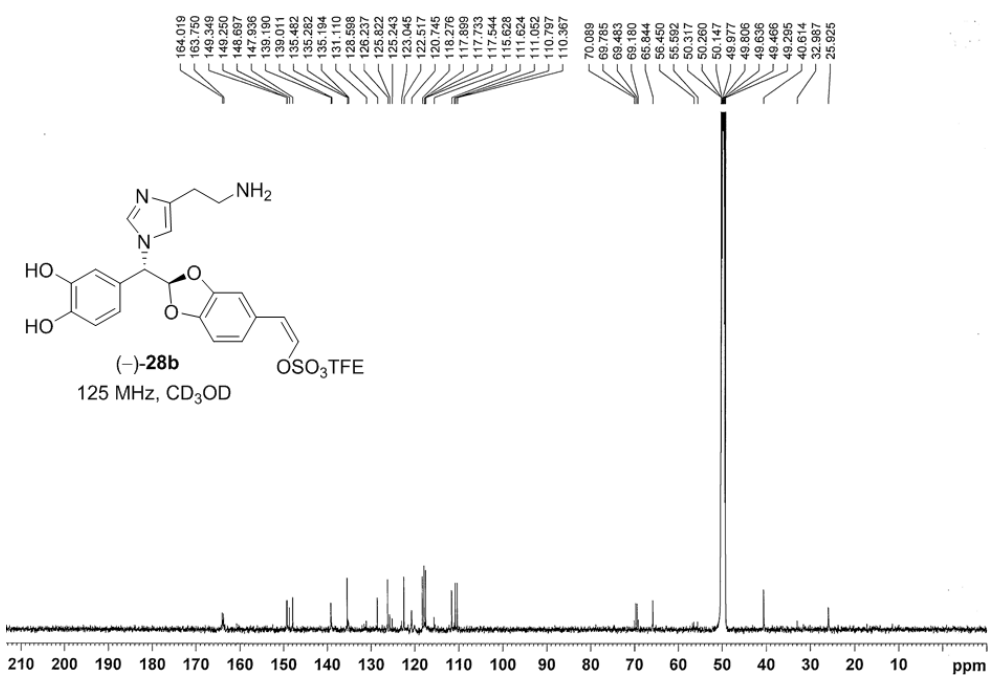

(−)-28a
800 MHz, CD3OD

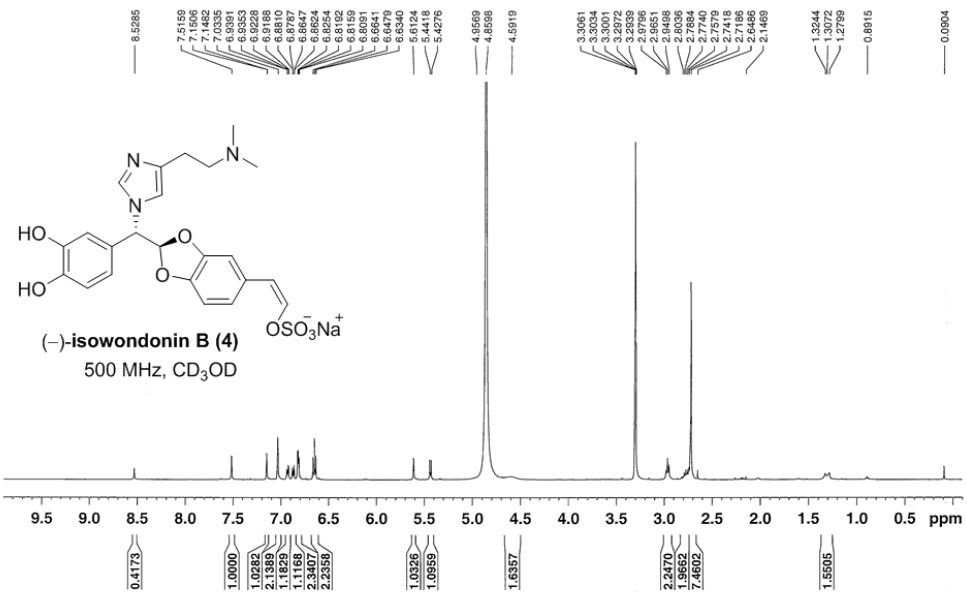

(−)-28a
200 MHz, CD3OD

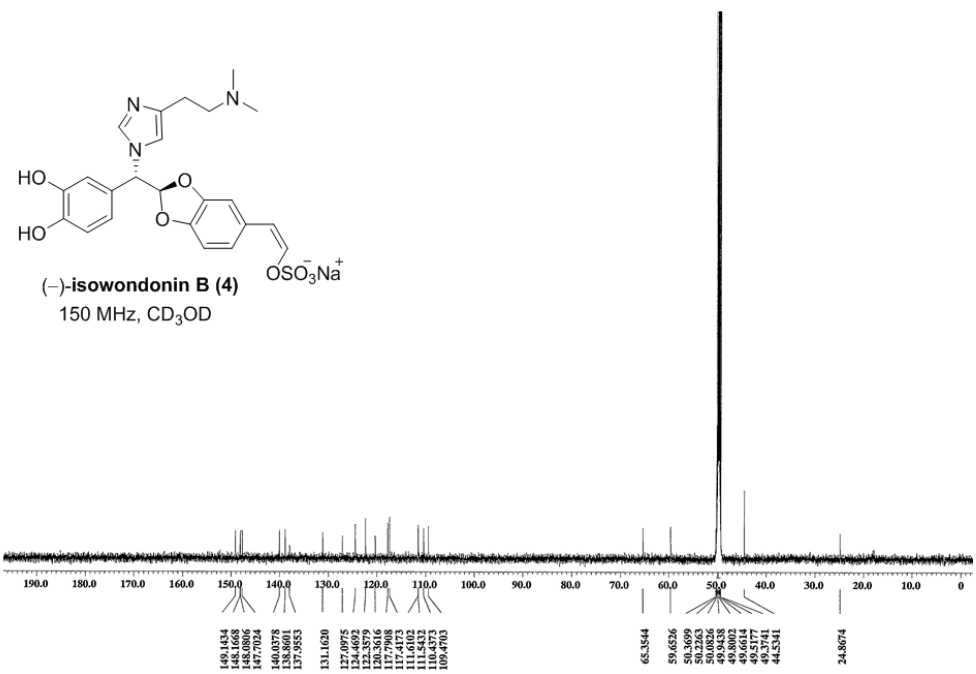

(−)-isowondonin A (3)
600 MHz, CD3OD
HCOOH

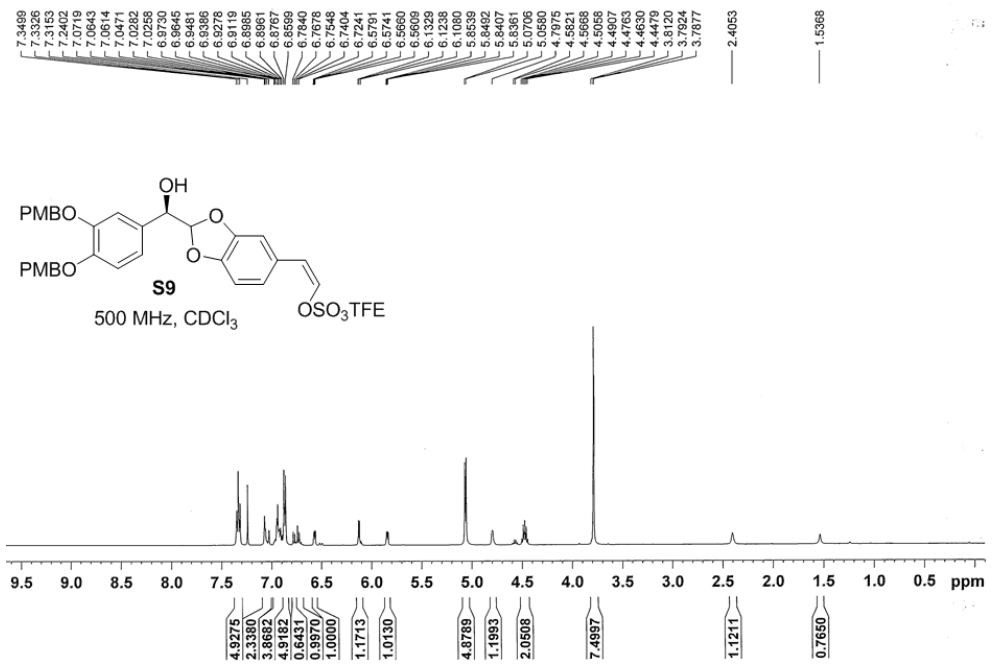

(−)-isowondonin A (3)
150 MHz, CD3OD

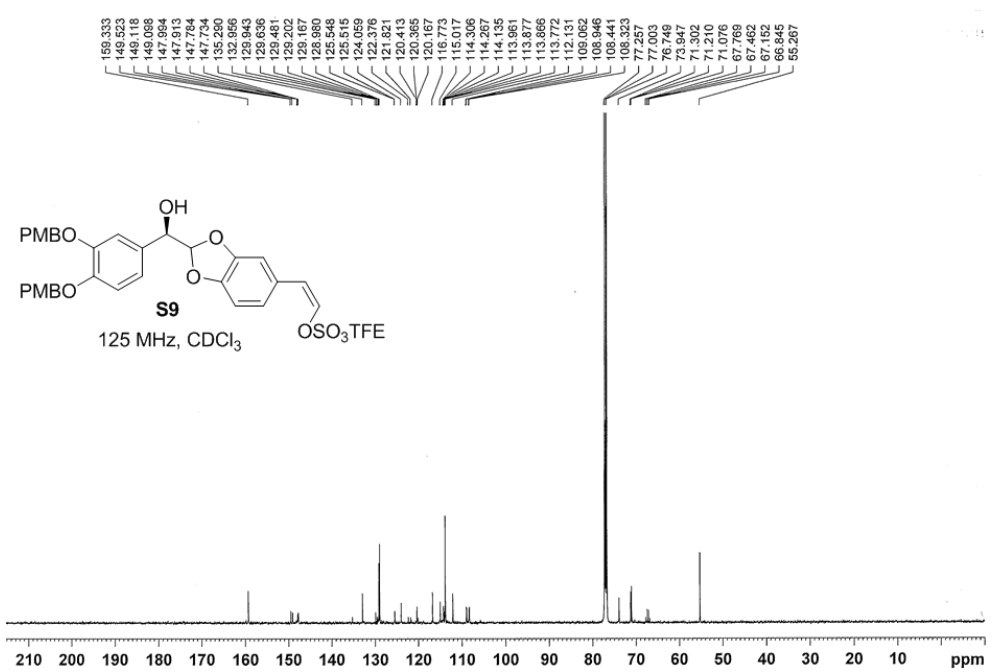

(−)-28b
500 MHz, CD3OD
OSO3TFE
ppm

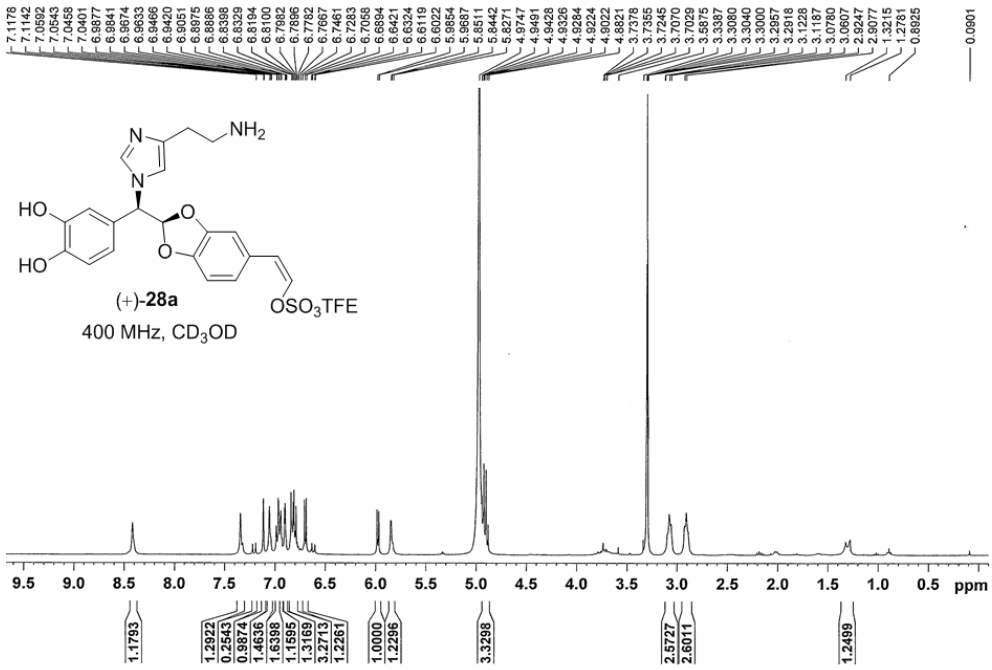

(−)-28b
125 MHz, CD3OD
OSO3TFE
ppm

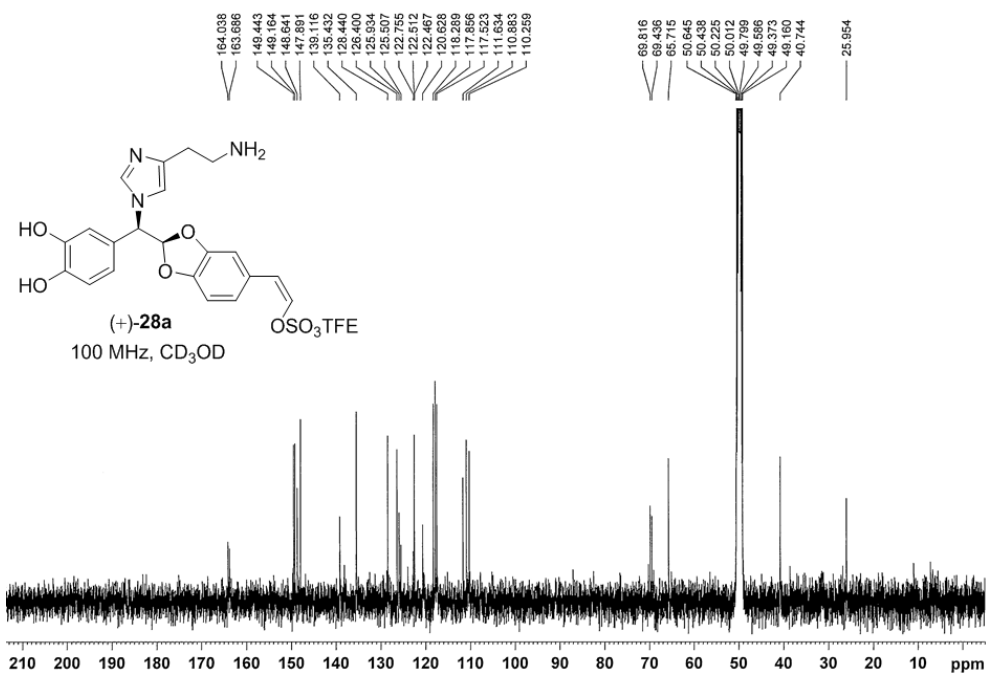

(−)-isowondonin B (4)
500 MHz, CD3OD
ppm

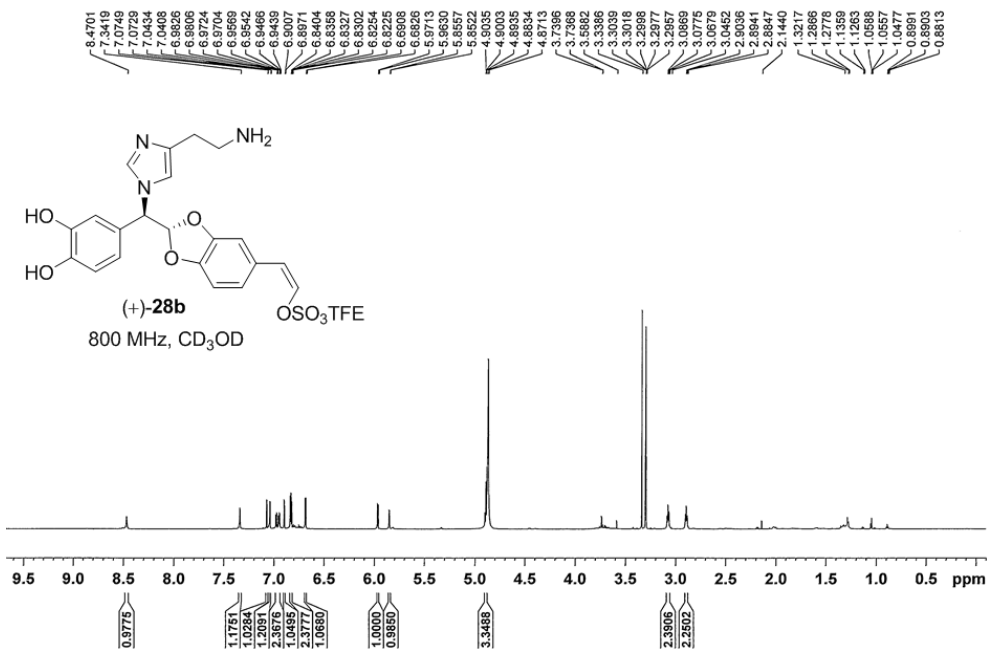

(−)-isowondonin B (4)
150 MHz, CD3OD

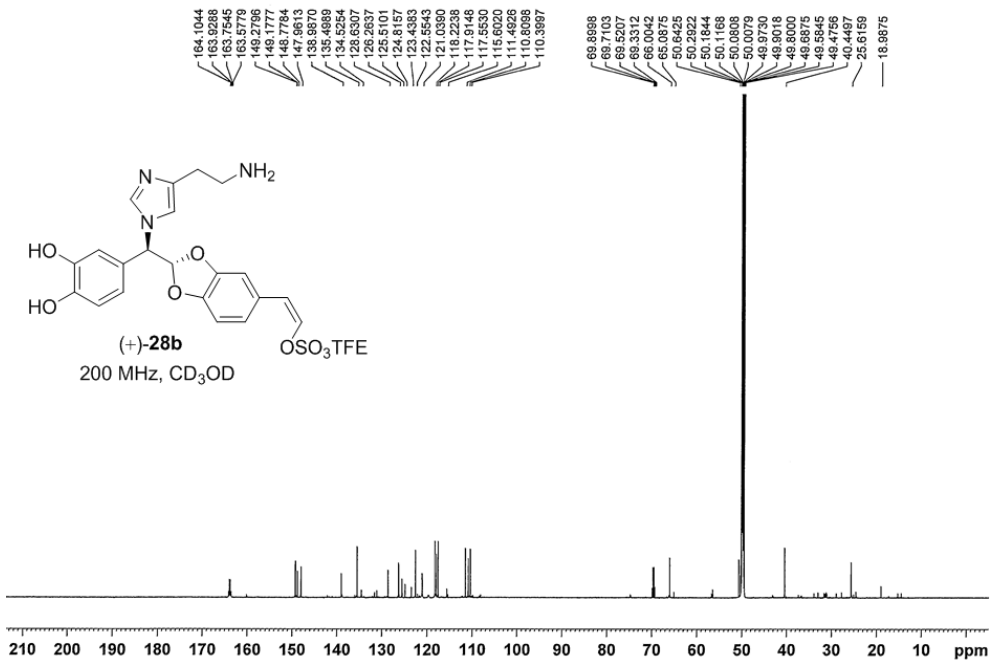

7.3499
7.3326
7.3153
7.2402
7.0719
7.0643
7.0614
7.0471
7.0282
7.0258
6.9730
6.9645
6.9481
6.9386
6.9278
6.9119
6.8985
6.8961
6.8767
6.8599
6.7840
6.7678
6.7548
6.7404
6.7241
6.5791
6.5741
6.5660
6.5609
6.1329
6.1238
6.1080
5.8539
5.8492
5.8407
5.8361
5.0706
5.0580
4.7975
4.5821
4.5668
4.5058
4.4907
4.4763
4.4630
4.4479
3.8120
3.7924
3.7877
2.4053
1.5368
OH
PMBO
PMBO
O
O
S9
500 MHz, CDCl3
OSO3TFE
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.9275
2.3380
3.8682
4.9182
0.6431
0.9970
1.0000
1.1713
1.0130
4.8789
1.1993
2.0508
7.4997
1.1211
0.7650

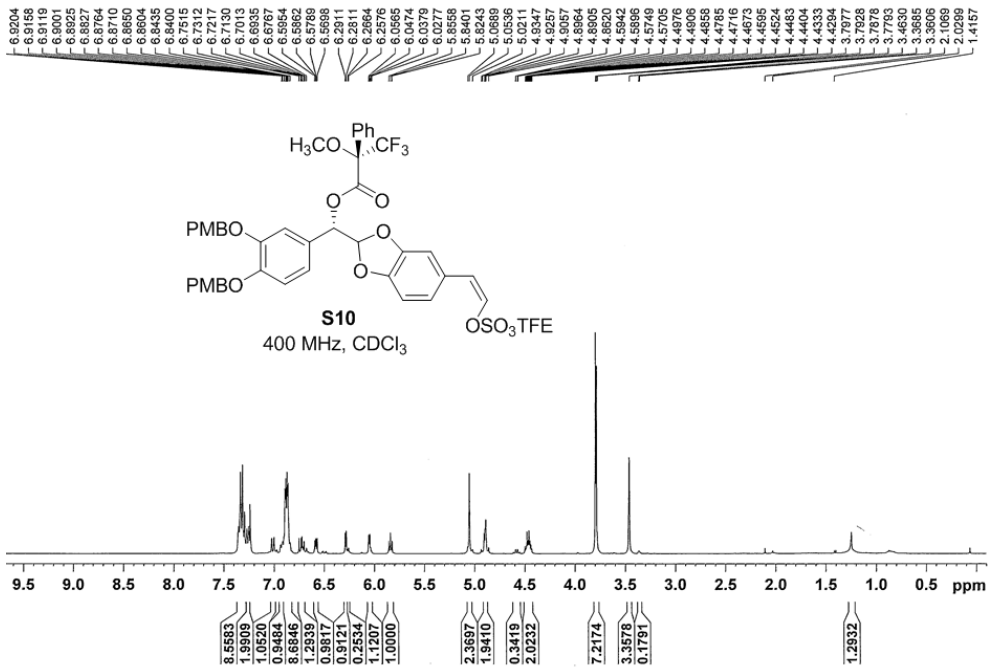

159.333
149.523
149.118
149.088
147.984
147.913
147.784
147.734
135.290
132.956
129.943
129.636
129.481
129.202
128.167
128.980
125.548
125.515
124.059
122.376
121.821
120.413
120.365
120.167
116.773
115.017
114.306
114.267
114.135
113.961
113.877
113.866
113.772
112.131
109.062
108.946
108.441
108.323
77.257
77.003
76.749
73.947
71.302
71.210
71.076
67.769
67.462
67.152
66.845
55.267
OH
PMBO
PMBO
O
O
S9
125 MHz, CDCl3
OSO3TFE
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

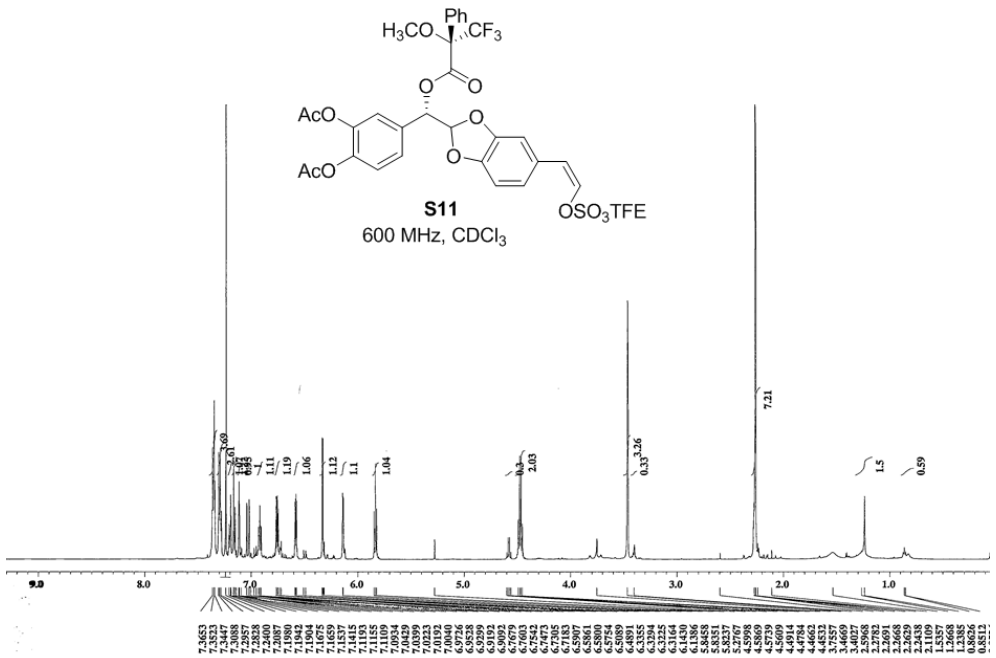

(+)-28a
400 MHz, CD3OD
OSO3TFE

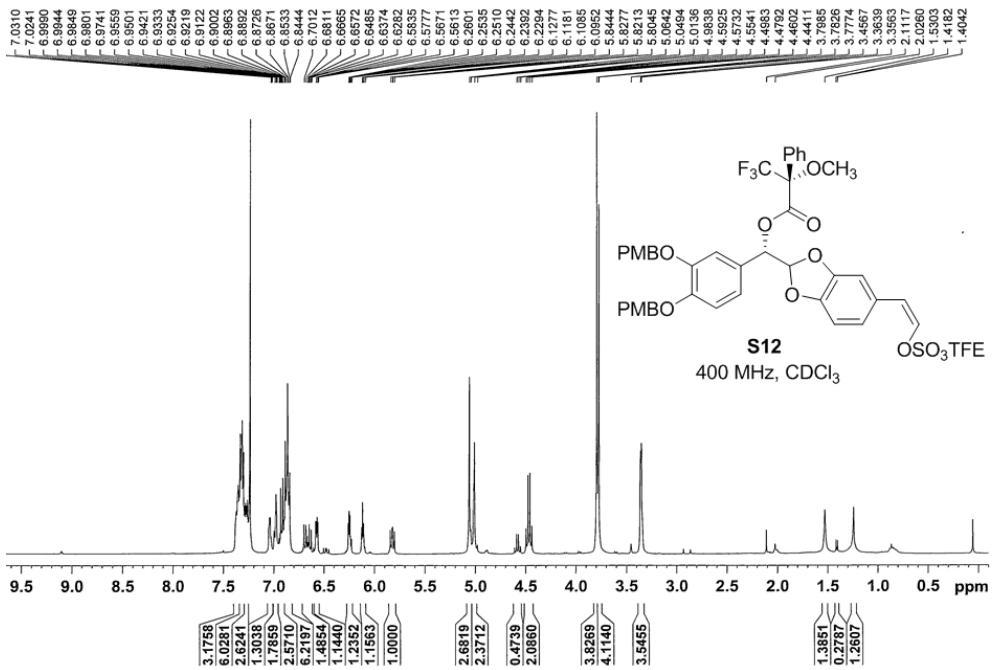

(+)-28a
100 MHz, CD3OD
OSO3TFE

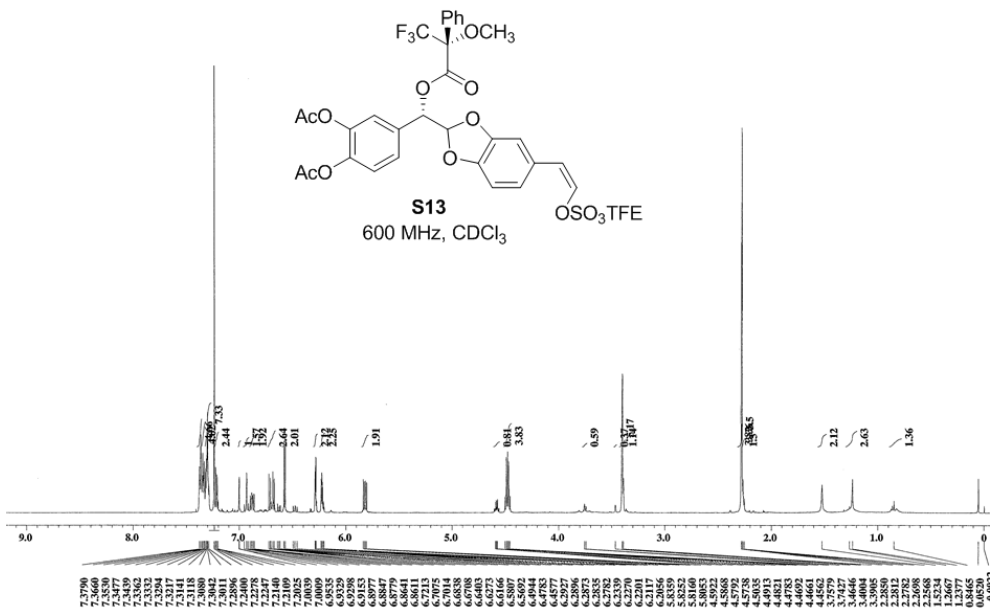

(+)-28b
800 MHz, CD3OD
OSO3TFE


(+)-28b
200 MHz, CD3OD
OSO3TFE


S10
400 MHz, CDCl3


S11
600 MHz, CDCl3


PMBO
PMBO
OSO3TFE
S12
400 MHz, CDCl3
ppm


AcO
AcO
OSO3TFE
S13
600 MHz, CDCl3

국 문 초 록

Wondonins와 isowondonins은 독특한 구조를 가진 해양천연물로서 five-membered acetal ring과 styryl sulfate로 구성된 dimeric dihydroxystyrenyl group을 주된 골격으로 가지고 있다. 특히, Wondonins는 뚜렷한 세포 독성을 가지지 않음과 동시에 bFGF 혹은 hypoxia가 유발된 human umbilical vein endothelial cells의 혈관 생성을 억제하는 것으로 알려져 있다. 따라서 해당 해양천연물은 새로운 angiogenesis inhibitors로서의 발전 가능성을 충분히 지니고 있으며, 근본적으로 천연 자원으로서의 양적 한계에 부딪힐 수 밖에 없기 때문에 해당 천연물의 효율적 합성 방법에 대한 연구가 필수적인 상황이다.

본 저자는 특이적인 imidazole 구조를 가지는 해양 알칼로이드 천연물인 wondonins과 isowondonins의 전합성을 최초로 성공하였다. 이를 위해 *E*/*Z* 구조 선택적인 styryl sulfate의 합성법과 imidazole의 위치 선택적 alkylation 방법을 개발하여 (±)-wondonins와 (±)-isowondonins의 라세믹 합성을 완성하였다. 해당 합성 경로는 예상 가능한 생합성 경로를 바탕으로 고안하였다. 더 나아가, Noyori asymmetric hydrogenation 방법을 라세믹 합성 경로에 적용하여 isowondonins의 입체 선택적 전합성을 완료하였다. 합성한 isowondonins의 실제 ECD 값과 계산값을 비교하여 isowondonin의 absolute stereochemistry를 밝혀내었다.

주요어: Angiogenesis, *E*/*Z*-Selective styryl sulfate formation, Regioselective imidazole alkylation, Noyori asymmetric hydrogenation, Total synthesis

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